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<i>Contents</i>	age
Changing Views on Heart Failure. John McMichael	
HERBERT A. PERKINS, JÖHN J. ÖSBORN AND FRANK GERBOOT.  A Study of Combined Mitral and Aorric Stenosis. Joseph F. Unio Hio, Kampta P. Sinha, Labberto Bentivocijo and Harry Goldberg	
Diagnosis of Chronic Aorto-Iliac Occlusive Arterial Disease. Engage A. Hines.	
Clinical Manifestations of Pulmonary Blastomycosis. Robert S. Americatus Pulmonary Afreolar Proteinosis: Report of Three Cases. Joseph C. Stenacki,	
Importance. Milton S. Sacks, Alexander S. Wiener, Elsa F. Jahn, Carrott I., Sputting and Lester J. Unger.  Recent Developments in the Laboratory Diagnosis of Syphilis. Warphild Garson	
Renal Failure in Laennee's Cirrhosis of the Liver. I. Description of Binical and Laboratory Features. Solomon Papper, Joseph L. Belsky and Kenneth H. Bleifer	
The Incidence of Myocardial Infarction in Portal Cirrhosis, Wilson C. Grant, Fred Wasserman, Paul L. Robensky and Robert V. Thomson	
Case Reports:  Blastomycosis Meningitis: Report of a Case Successfully Treated with Amphoterioin B. EVERETT J. CARMODY and WILLIAM TAPPEN	
K. Myers  Amyloidosis Secondary to Chronic Ulcerative Colitis. Irving A. Warren, Isaias Stateler and Sidney D. Köbernick	
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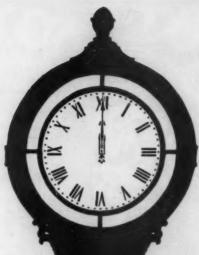
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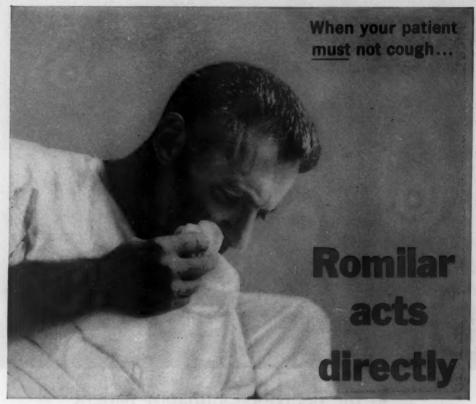
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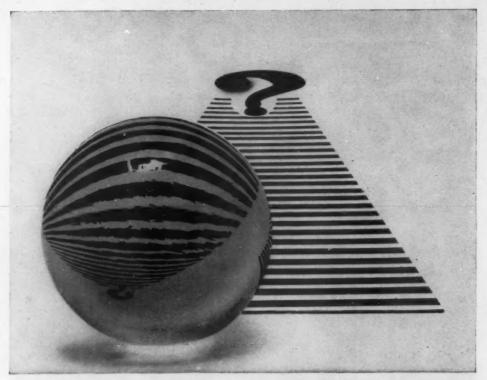
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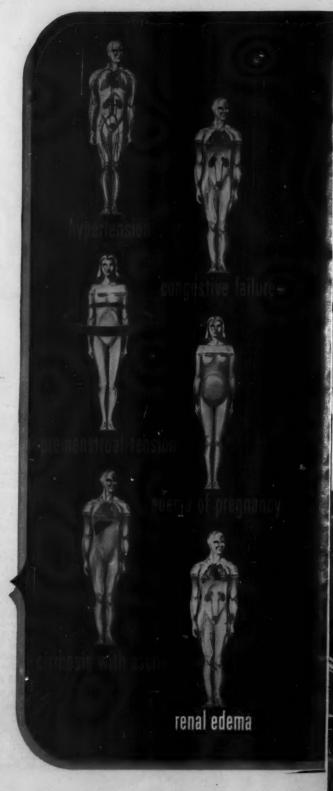
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Desoxycholic Acid (50 mg.)—a choleretic, also is a chemically pure bile acid and stimulates an increased flow of bile, lowers surface tension and stimulates peristalsis. By emulsifying fat globules, desoxycholic acid aids the digestive action of the fat-splitting enzyme, lipase. Decholin and desoxycholic acid thus favorably influence the constitution and the movement of the intestinal contents.

Dioctyl Sodium Sulfosuccinate (50 mg.) is a wetting agent which lowers surface tension and aids the penetration of intestinal fluids into the fecal mass, providing a moist stool of normal consistency.

**EFFEOTIVE:** Bile influences the constitution as well as the movement of the intestinal contents. The ingredients of major importance are Decholin and desoxycholic acid which increase the flow of bile, lower surface tension, promote emulsification and absorption of fats and mildly stimulate intestinal peristalsis. With dioctyl sodium sulfosuccinate, a good therapeutic effect can be obtained without the danger of toxicity or decreasing effectiveness even when used regularly.

**SAFE:** Clinical evidence indicates that the constituents of DECHOTYL cause no systemic sensitivity, drug accumulation, habituation or interference with nutrition. Orally, in therapeutic amounts, DECHOTYL is without significant toxic effect. The only side effect following oral administration is diarrhea if the dosage is excessive.

**Dosages** Average adult dose—Two Trablets\* at bedtime. Some individuals initially may require 1 to 2 Trablets three or four times daily. Contraindications: Biliary tract obstruction; acute hepatitis.

Available: TRABLETS, coated, yellow, trapezoid-shaped; bottles of 100.



# waterloo for an ulcer...

Napoleon exhibited ulcer symptoms through most of his adult life, yet he scorned medication for his everlasting "spasms of nervous origin." He ignored his infirmities with violent naïveté despite an intense interest in medical science. Thus, the classic hand-incoat pose may have been the result of his paroxysms of gastric pain that sliced "like the stab of a penknife."

When your patient is besieged with an ulcer, Robins provides you with an armamentarium sufficient to repel it.

frontal assault - If your tactics dictate Local Action, try ROBALATE, which is dihydroxy aluminum aminoacetate (0.5 Gm. per tablet or 5 cc.), an antacid of definitely superior efficacy.

encirclement - If you prefer to approach the ulcer Systemically, prescribe DONNATAL, the anticholinergic-antispasmodic-sedative with the timetested natural belladonna alkaloids and phenobarbital, a veteran campaigner without peer. FORMULA: hyoscyamine sulfate, 0.1037 mg.; atropine sulfate, 0.0194 mg.; hyoscine hydrobromide, 0.0065 mg.; and phenobarbital (1/4 gr.), 16.2 mg.

multi-pronged attack - If you relish the strategy of combining antacid and antispasmodic-anticholinergic effects, use DONNALATE. It combines one-half of a DONNATAL tablet with one ROBALATE, ideal allies for comprehensive ulcer therapy.

Victory will be yours.

A. H. ROBINS CO., INC. • RICHMOND, VA.

DONNALATE Robins



even
if your
patient
is a
lobscouser

he'll be under way again soon, once he's on

# **PARAFON**

for muscle relaxation plus analgesia

and in arthritis
PARAFON
with Prednisolone



McNeil Laboratories, Inc + Philadelphia 32, Pa.

prescribe Paration in low back pain-sprains-

Each Pararon tablet contains:

ARALLEN Chlorzoxazonet 125 mg

TYPENOT Acctaminophen 300 mg

Dosage: Two tablets t.i.d. or q.c.d.

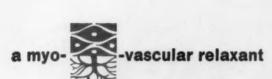
Each Pararon with Prendisoloni tablet contains: Parares S. Chlorzonazone 125 mg., Tylenot S. Acetaminophen 300 mg., and predisolone 1.0 mg.

Supplied: Tablets, wored, buff colored, bottles of 36. Precations. The precautions and contraindications that apply to all steroids should be kept in mid-when prescribing PARAFOR WITH PRODUSTOLORE.

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104015

NEW
from
Mead
Johnson



# selective peripheral action to relieve symptoms of arterial insufficiency<sup>1</sup>—

intermittent claudication
leg pain
coldness and numbness of extremities
in
Arteriosclerosis Obliterans
Diabetic Vascular Disease
Buerger's Disease
Thrombophlebitis

# VASODĪLAN'

Mead Johnson is proud to announce the availability of Vasodīlan, an unusual new compound with myovascular relaxant action. The unique myovascular action of this substance is manifested by selective relaxant effects on smooth muscle of the peripheral and cerebral vascular beds and of the uterus.

A major indication for VasopīLan is in the symptomatic treatment of peripheral vascular disease.

# brings blood to the deep tissues by direct action on the arterial wall<sup>1-3</sup>

with remarkable safety in recommended doses without adverse effects on coronary flow<sup>1,2</sup> without troublesome hypotension or tachycardia<sup>1,2</sup> without renal effects<sup>1,2</sup>

without renal effects."
without increase in gastric acidity<sup>2</sup>
without ganglionic blocking action<sup>1-3</sup>
without development of tolerance<sup>1</sup>

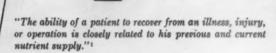
in illness

injury

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with

# Sustagen<sup>®</sup>

powder

...you can supply generous amounts of all known essential nutrients in convenient concentrated form. Your patient's recovery time is shortened, and your diet problems are simplified when you use Sustagen...

- as a complete liquid diet
- as a basis for soft or bland diets
- . to fortify other special diets

orally or by nasogastric tube . . . just add water

1. Halpern, S. L.: Ann. New York Acad. Sc. 62: 147-184 (Oct. 36) 1985.



# How many patients today complained about pain?



non-narcotic—pain relief equivalent to that of codeine

well tolerated in both acute and prolonged use

wide range of indications—general practice and the specialties

analgesia plus anti-inflammatory action

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

remember

Philadelphia 1, Pa.

Zactirin

Ethohentazine Citrate with Acetylsalicylic Acid. Wyeth

# ANTURAN

(Sulfingviszone GEIGY)

### High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosume agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid\*...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is, good.

### Clinically, ANTURAN

- · Prevents formation of new tophi
- Causes gradual absorption of old tophi
- · Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN is recommended. Detailed Information on Request

Yu. C. F., Buens. J. and G. Iman. 4. B. Artin. & Rheumat. 1.532, 1958.

Ansusan (Sulfinpyrazone SE(GY). Scored tablets of 100 mg. in bottles of 100 Burrazon pink (phenylburay - CF(GY).

Andeley New York

Ardsley, New York

# CONVENIENCE and ECONOMY

# TERRAMYCIN

# INTRAMUSCULAR SOLUTION

Initiation of therapy in minutes after diagnosis with new,

# COSA-TERRAMYCIN

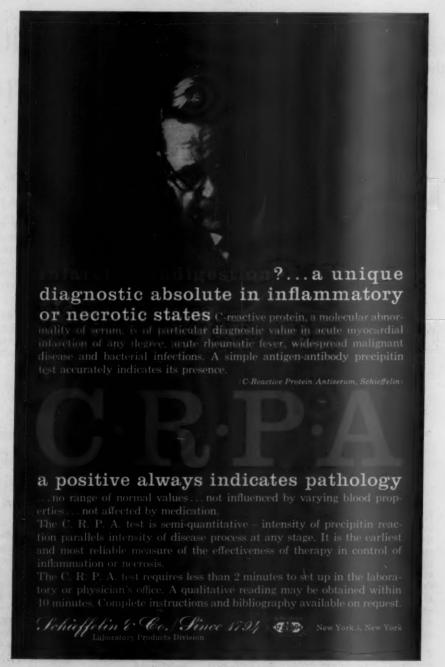
CAPSULES

Supply:

Terramycin Intramuscular Solution

Cosa-Terramycin Capsules

Cosa-Terramycin is also available as:





Roche announces the first major breakthrough in the prophylactic management of pain in angina pectoris

# Ten critical Marplan

# Marplan

clinically safer

• therapeutically more useful

a new, more active amine oxidase regulator which has proven highly valuable in the symptomatic relief of angina pectoris

In approximately 70% of cases, Marplan

- reduces the frequency of anginal attacks
  - improves exercise tolerance
  - lowers nitroglycerin dependence

1. What is Marplan? Marplan is a hydrazine derivative with marked potency in regulating the amine oxidase enzyme system. Already evaluated in over 3500 patients, Marplan has demonstrated marked beneficial effects in the treatment of angina pectoris. Evidence to date indicates that Marplan may also be therapeutically valuable in a number of other important acute and chronic medical conditions. Chemically, Marplan is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine.

2. What is the effect of Marplan in angina pectoris? Continued prophylactic administration

of Marplan provides symptomatic relief—in the form of pain control and reduced nitroglycerin requirements—in approximately 70 per cent of cases. 1-3 "Excellent effects with relatively small doses" are reported in a group of 31 patients with angina pectoris. In that study, Marplan "afforded greater relief than any other compound in our experience." To date, Marplan prophylaxis has been evaluated in a total of 238 anginal cases. The response rate was 72.7 per cent, with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state. 1

- 3. What is the effect of Marplan on blood pressure? Marplan should not be used as a hypotensive agent. The possibility of postural hypotension, though relatively infrequent, must be borne in mind.
- 4. What type of angina case is particularly responsive to Marplan prophylaxis? Marplan has been evaluated in angina of varying severity. It is felt, however, that optimum benefit will be derived in moderately severe to intractable cases.
- 5. Is the antianginal effect of Marplan the same as its antidepressant action? Marplan is unique in that it exhibits two distinct primary effects: its antianginal action, while biochemically related, is clinically separate from its antidepressive effects.
- 6. How can one compound have two such seemingly dissimilar effects? The mechanism of action of Marplan and of the other amine oxidase regulators is not yet fully defined. Marplan's pharmacologic effects are secured indirectly: By regulating amine oxidase levels; it inhibits the breakdown of serotonin, norepinephrine and other biologically active amines. In animal experiments, serotonin infusion of the heart muscle produces an increase in the ratio of coronary blood flow to coronary vascular resistance.<sup>4</sup>

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# al questions define the scope of anprophylaxis in angina pectoris

7. How should Marplan be given? The usual starting dose is 30 mg daily to be given in single or divided doses. The patient should be observed carefully and individual dosage adjustment made according to response. Many patients will respond quickly to the initial dose of 30 mg daily, and the dosage should then be reduced to 10 or 20 mg daily (or less) for maintenance therapy. In some patients beneficial effects may not be observed for three or four weeks. Since daily doses larger than 30 mg may cause an increase in side effects, such as hypotension and constipation, it is not recommended that higher dosages be employed.

8. What are the precautions? All patients treated with hydrazine derivatives should be kept under close medical supervision. While there is no definite knowledge of a hazard with Marplan, use of this class of agent should be discontinued at the first sign of jaundice or impaired liver function. Periodic liver function tests are advised during hydrazine therapy. These drugs are contraindicated in patients with a history of previous liver disease or impaired liver function. In patients with impaired kidney function, Marplan should be used cautiously to prevent accumulation and should not be used in epileptic patients. Patients receiving a hydrazine in conjunction with drugs such as alcohol, ether, barbiturates, meperidine, cocaine, procaine, and phenylephrine should be more closely supervised.

9. What are the side effects, if any? In one of the largest bodies of clinical material for this new class of drugs, Marplan shows one of the lowest recorded incidences of side effects. Particular attention was focused on attempts to define as precisely as possible amine oxidase inhibitor side effects on a wide range of organs, including liver and bone marrow. Extensive clinical studies have revealed no jaundice or liver damage attributable to Marplan. Nevertheless, since Marplan is an amine oxidase inhibitor, the

same precautions should be observed with Marplan therapy as with other amine oxidase inhibitors. Since Marplan is a potent therapeutic agent affecting many enzyme systems of the body, side effects may be expected to occur in a certain percentage of cases. Side effects have rarely been severe enough to necessitate discontinuance of Marplan therapy. However, as with all agents of this type, the patient should be observed for signs of orthostatic hypotension, complaints of dizziness and vertigo, constipation, overactivity, jitteriness, insomnia, peripheral edema, weakness, fatigue, dryness of the mouth, blurred vision and skin rashes.

10. How can patients be transferred from their present anginal prophylaxis? Initially the established nitrite regimen should be maintained, while simultaneously placing the patient on a daily dose of 30 mg Marplan. The patient is to be observed carefully and nitrite intake decreased as pain episodes diminish. Response to Marplan prophylaxis may be delayed for several weeks.

# Marplan

Supplied: 10-mg tablets in bottles of 100 and 1,000.

References: 1. Clinical reports on file, Roche Laboratories, 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, 8399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. C. W. Crumpton, et al., Conference on Amine Oxidase Inhibitors, New York City, November 20-22, 1958.

MARPLANT.N. - brand of isocarboxazid



ROCHE LABORATORIES

Division of Hoffmann-LaRoche Inc . Nutley 10 . N.J.

Miltown in continuous
release capsules

Meprospan

Meprospan

the <u>24-hour</u> tranquilizer

safe, continuous relief of anxiety and tension ... all day ... all night

Supplied: 200 mg. continuous release capsules of Miltown (meprobamate, Wallace) in bottles of 30. Literature and samples on request

WALLACE LABORATORIES . New Brunswick, N.J.

CME-9700

# New Enzyme-controlled antifungal therapy to meet the growing challenge of Monilial Vaginitis

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY—Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females!—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

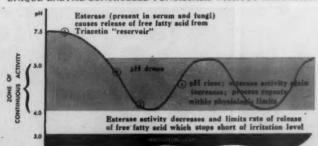
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.<sup>2</sup> Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.<sup>3</sup>

Other advantages: No monilial resistance demonstrated<sup>4</sup> / prolonged duration of activity<sup>4</sup> / nonsensitizing / nonirritating / nonstaining / odorless.

# "VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION3.6





AYERST LABORATORIES

New York 16, N.Y. · Montreal, Canada



Indications: specific in monilial vaginitis...adjunctive in trichomoniasis...also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

Usual Dosage: 2 to 4 grams daily. Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Ideon, B.: Drug & Cosmetic Industry \$4:30 (Jan.) 1959.

2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. 28:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.



common denominator: a. p. People worlds apart-plumber, pediatrician of Peritrate 20 mg. q.i.d. all remain normally active with fewer, less severe attacks, clubwoman, counterman - have one thing in common: angina pectoris. On "basic therapy" increased exercise tolerance, and reduced nitroglycerin dependence.

At times, however, personality problems, underlying apprehensions, emergency situations, or unpredictable schedules call for "basic therapy" plus individualized treatment. Broad coverage protection for each patient is afforded by Peritrate formulations in terms of Adaptable Prophylaxis:

Peritrate with Aminophylline, q.i.d. . . . Peritrate Sustained Action, b.i.d. . . . Peritrate with Nitroglycerin, p.r.n. . . . Peritrate with Phenobarbital, q.i.d.

.....for the apprehensive patient ...... for congestive failure .... for convenient 24-hour protection ...... to relieve the acute attack

# angina pectoris & postcoronary convalescence: to increase coronary circulation in

of myocardial damage and prevent ensuing anginal episodes. Peritrate, a selective longacting vasodilator, may prove to be the drug of choice because it increases coronary flow After a coronary, aiding the development of collateral circulation serves to reduce effects without a significant fall in blood pressure.

clinical supply of Peritrate 20 mg. is available from Dept. A.W.: Warner-Chilcott,



Peritrate

MORRIS PLAINS, N.J.

# PROTECTS AGAINST ANGINAL ATTACKS

RUSSEK: PETN is "... the most effective drug currently available for prolonged prophylactic treatment of angina pectoris." Prevents some 80% of anginal attacks.

# EASES CARDIAC TENSION

RUSSEK: "I favor ATARAX [as the tranquilizer for the anxious cardiac]... because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."<sup>2</sup>

PETN + ATARAX

# CARTRAX

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX)3 to 4 times daily. When indicated this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.



New York 17, N. Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being

# now potent tranquilizer therapy is safer than ever



Virtual teacher of  $M_{22}$  is a magnitude of the problem of the second of the second

MELLARIL is virtually free
of such toxic effects as
• jaundice
• Parkinsonism
• blood dyscrasia

Thioridazine [MELLARIL] is as effective of the dest available phonothiasine, but with appreciative last toxic effects than those demonstrated with other phenothiasinal. The draw appears to represent major additional title safe and effective treatment of a wide range of psychological disturbance, seen daily in the last or by the reneral machinesis.



Mellaril

Shirth of the Sangalizer's safer at all gosage levels

#### remarkable lack of side effects

In more than 3,000 carefully-followed patients, Mellaril has been almost completely free of such major side effects as jaundice, extrapyramidal symptoms, Parkinsonism, blood dyscrasia, dermatitis—even when given in quantities far in excess of the usual dosage.

#### "POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs." <sup>2</sup>

#### NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism." 8

#### SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in

any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."4

#### ABSENCE OF SIGNIFICANT SIDE EFFECTS

"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."

#### MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine." <sup>5</sup>

#### NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug." 6

Mellaril

specific, effective tranquilizer + safer at all dosage levels



#### a new advance in tranquilization: greater specificity of tranquilizing action plus fewer side effects

is-

Of 109 phenothiazines synthesized by Sandoz, Mellaril was selected as the most promising on the basis of extensive evaluation. The presence of a thiomethyl radical (S-CH<sub>2</sub>) in the position conventionally occupied by a halogen in other phenothiazines is unique and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.

PSYCHIC RELAX FRON

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SYMPATHETIC AND PARASYMPAT STO NERVOUS STEEL Interest of temperature regulation

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- 2 Less "spill-over" action to other brain areas hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.
- 3 A notable absence of extrapyramidal stimulation.
- 4 Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.
- 5 Virtual freedom from toxic effects jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

Mellaril



#### excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY"... produced extremely satisfactory results in the broad therapeutic range represented in this series."3

POTENT AGENT "... appears to be a potent agent in the symptomatic management of a variety of psychiatric states." 4

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent....

It is effective in a variety of psychiatric disorders, including schizophrenic reactions.... The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome." 6

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life... were treated with Mellaril at the dosage level of 10 mg. three times daily.

In 94 such patients, 83 obtained an excellent therapeutic response." 8





"... extremely satisfactory results..."
in a clinical spectrum ranging from
minor nervous disorders to
severe psychotic disturbances

#### RESULTS WITH MELLARIL IN 194 PATIENTS3

#### ACUTE PSYCHOTICS

83% satisfactory effect

Some cases had complete remission of symptoms. Most were able to return home to useful occupations.

#### CHRONIC PSYCHOTICS

68% satisfactory effect

Relief of symptoms in cases permitted easier management and a return to a more or less useful life.

#### NEUROTICS

57% satisfactory effect

Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

DIAGNOSTIC CATEGORY	IMPROVED %	SATISFACTORY	SATISFACTORY %	UNSATISFACTORY
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC .	75	25	50	25

Mellaril

specific, effective manguillizer + safet at all dosage levels



#### a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
	ADULTS	
Mental and Emotional Disturbances:		
MILD – where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE — where agitation exists in psychoneurosis, alcoholism, intractable pain, senlity, etc.	25 mg. t.l.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory Hospitalized	100 mg. t.i.d. 100 mg. t.i.d.	200-400 mg. 200-800 mg.
	CHILDREN	
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Outfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. 115:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- · controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- · virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- · minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- · increased specificity of action results in greater safety at all dosage levels



Mellaril



#### ADVANCED ELECTROCARDI-OGRAPHY COMPLEX ARRHYTHMIAS

L. N. KATZ, R. LANGENDORF and A. PICK

MICHAEL REESE HOSPITAL AND MEDICAL CENTER

December 7-11, 1959

Differential diagnosis of arrhythmias based on fundamental physiological concepts. Tuition: \$100.00.

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Millown + anticholinergic

relieves anxiety and tension
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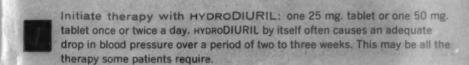
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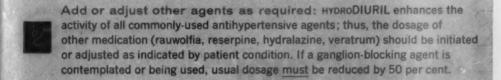
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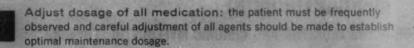


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FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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Sugar-coated Tablets of 2 mg.

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'Myleran' has been reported to induce remissions, lasting up to two years, in chronic myelocytic leukemia. In addition to the decrease in total white cell count and a selective reduction of immature myeloid cells, it usually gives, early after its administration, a rise in hemoglobin level and pronounced subjective improvement.

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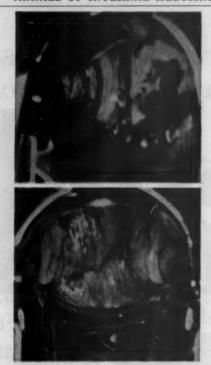
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Two potencies that will meet the needs of your patients: PMB-200 — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe PMB-400 — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

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TABLETS CANDIDIASIS is especially serious in diabetics . . . during pregnancy . . . in the debilitated . . . and when broad spectrum antibiotics have been administered in high dosage, with or without concurrent administration of cortisone or related steroids.

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SUPPLIED: Each Mycostatin Vaginal Tablet – Individually foll wrapped contains Mycostatin, 100,000 units, and lactose, 0.93 Gm. Packages of 15 with applicator. Also available: Mycostatin Oral Tablets . . . Ointment . . . Dusting Powder . . . Powder for Suspension . . . Cream.

REFERENCES: 1. Lee, A.F., and Kelfer, W.S.: Northwest Med. 53:1227 (Dec.) 1954. e 2. Caruso, L.J.: New York J. Med. 58:1688 (May 15) 1958. e 3. Pace, H.R., and Schantz, S.I.: J.A.M.A. 162:268 (Sept. 22) 1955.

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restores your depressed patient to purposeful reality

sad, worried, guilt-ridden, nervous, gloomy thoughts, feelings of uselessness, appetite and sleep troubles, lethargic

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No significant reports of toxicity to liver, kidneys or blood<sup>1-3</sup> in thoseands of cases to date

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Antidepressant activity within the first few days; complete recovery occurs within 2 to 6 weeks.

correctively

Removes the depression itself, does not merely mask the symptoms as do tranquilizers and sodatives.

Nardil is indicated in the office treatment of all mild to severe depressions; in those related to childbirth, menopause, old age, or those caused by stress situations; when there is a past history of depressed periods, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

Dosage: One tablet three times a day.

The above dosage should be maintained until remission of symptoms is achieved which may require 2 to 6 weeks. Dosage should then be reduced to a maintenance level of one or two tablets a day.

Supplied: 15 mg. orange-coated tablets, bottles of 100.

References: 1. Sains, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, Ans. New York Acad. Sc. (in press) 1959. 2. Thal, N.: Camulative Index of Antidepressant Medications, Dis. Nerv. System 20:197 (May) 1959. 3. Saunders, J. C.; Roukems, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelsine, Am. J. Psychiat. (in press) 1959.





for consistent therapeutic response



In all conditions requiring substitution therapy with thyroid bormone

Supplied in 4, 42, 1, 2 and 5 grain strengths.

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When your overweight patient is listless and lethargic—**DEXEDRINE**†

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\*Clinical Report on file at the Department of Medical Research, Winthrop Laboratories.

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1406M

stop as well as prevent nausea and vomiting

Tigan

now in oral, parenteral, and suppository forms effective but not "side effective"

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),1 a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.1 In extensive clinical studies2-14 Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimu-



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#### no special precautions no known contraindications

in nausea/vomiting of gastrointestinal disorders Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients; 13 "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure." 18

in nausea/vomiting of pregnancy

No evidence of sedation or other side effects<sup>12</sup> observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.<sup>12</sup>

in nausea/vomiting of radiation sickness

Protected with Tigan "... not one patient had to discontinue [deep radiation] treatments..."5

in nausea/vomiting of drug administration "...large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."

III santiemetic antinauseant

no sedative properties no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, orally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

How Supplied: Tigan capsules, 100 mg, blue and white — bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)—boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6 and 25.

References: 1. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., in press. 2. W. B. Abrams, I. Rosefi, J. Kaulman, L. Goldman and A. Bernstein, to be published. 3. I Rosefi, J. Kaulman, L. Goldman and A. Bernstein, I. Reverk Beth Israel Hosp., 9:189, 1938. 4. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan. New York City, May 15, 1959. 5. J. A. Lucinian ibid. 6. D. W. Moiander, ibid. 7. B. I. Shuder, ibid. 8. W. S. Derrick ibid. 9. B. Woifson and F. F. Foldes, ibid. 10. L. McLaughlin, ibid. 11. Reports on file, Roche Laboratories. 12. Personal communications. 13. W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 14. H. E. Davis, ibid.

TIGAN<sup>T-M</sup>- Hydrochloride-4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride ROCHE®



Division of Hoffmann-La Roche Inc. Nutley 10, N. J.



- Prompt remission of symptoms
- Bleeding and frequency of stools sharply reduced
- Healing of rectal mucosa within a month in most cases
- Can be given safely over long periods of time

At zulfidine 8 BRAND OF SALICYLAZOSULFAPYRIDINE

the most
valuable drug
in the
treatment of

Ulcerative Colitis "The most widely accepted sulfonamide preparation today for the therapy of chronic ulcerative colitis is salicylazosulfapyridine (Azulfidine)"

Hightower, N.C., Jr., and others: Am. J. Digest, Dis.: 3:931 (Dec.) 1958

Also valuable in treatment of regional enteritis and other forms of colitis

Pharmacia Laboratories, Inc.



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Specific in Depression

## does

Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe as in mild cases

Achieve therapeutic benefit with minimal risk of serious side reaction

Indications for Tofranil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofranil (brand of imipramine HCI) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

## ....not a MAO inhibitor

## does not

Inhibit monoamine oxidase either in brain or liver with its associated risks

Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.



Geigy, Ardsley, New York

Geigy

## HYPOTENSION

raise and maintain blood pressure with knowledge that "distressing side effects, such as thrombophlebitis or tissue slough, do not occur."<sup>1</sup>

INJECTION

## ARAMINE

BITARTRATE

#### for vasopressor action with a choice of routes

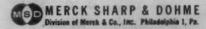
ARAMINE has gained rapid acceptance as a practical vasopressor for combatting hypotension due to hemorrhage and surgical complications. Administer ARAMINE by subcutaneous or intramuscular injection, by intravenous infusion or by direct intravenous injection as the clinical situation demands. Extravascular deposition has not resulted in tissue slough, necrosis or thrombophlebitis.<sup>14</sup> Expect a smooth, sustained vasopressor effect with no secondary fall in blood pressure. There are no reports of tachyphylaxis or hyperglycemia.

ARAMINE is equally valuable in treatment of shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease.

supplied:in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references:1, Circulation 13:834, June 1956. 2. Am. J. M. Sc. 200:357, Oct. 1955. 3. Circulation 18:1096, Dec. 1957. 4. J.A.M.A. 163:1482, April 20, 1957.

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## reduces anginal attacks

protects against pain by sustained coronary vasodilatation and control of complicating and triggering emotions

reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance

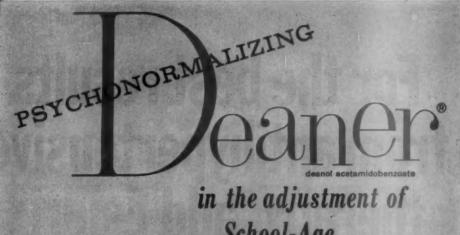
Supplied: Tablets, vials of 50. Each tablet contains 200 mg. of meprobamate and 10 mg. of pentaerythritol tetranitrate.

EGUANTIRA

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

Hyeth

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School-Age Problem Children

when intelligence is masked by behavior problems, in the absence of organic cause

- Improves scholastic performance...
- Lengthens attention span...
- Improves social adaptability...
- Decreases irritability

#### Dosage

75 mg. (3 tablets) in the morning is the recommended starting dose. After two weeks, or whenever satisfactory improvement has occurred, a reduced dose may maintain this improvement in some cases; however, optimal response has been reported in most children on maintenance doses ranging from 75 mg. (3 tablets) to 150 mg. (6 tablets) per day.

#### Contraindications

'Deaner' therapy is contraindicated only in grand mal epilepsy and in mixed epilepsy with a grand mal component.

eaner may be given with safety to patients with previous or current liver disease, kidney disease, or infectious diseases.



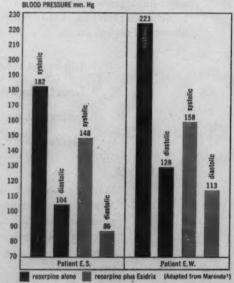
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(hydrochlorothlazide casa)
THE ANTIHYPERTENSIVE POTENTIATOR

Esidrix, through its unique effect on body salts,\* provides a physiologic environment in which antihypertensive drugs work best. Thus Esidrix, when added to any treatment program:

- Safely reduces blood pressure to the lowest levels yet achieved with oral therapy.
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- Promotes diuresis in patients with edema.

Potentiating Effect of Esidrix on Serpasil BLOOD PRESSURE mm. Hg



\*Esidrix is at least 10 times more active than chlorothiazide and greatly increases sodium and chloride excretion; however, it has no more effect on potassium excretion than does chlorothiazide.

Esidrix-Serpasil gives excellent results in hypertensive patient with tachycardia: slows heart rate and lowers blood pressure to within normal limits two weeks after therapy.



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Esidrix-Serpasil lowers blood pressure more effectively: Blood pressure response is better with Esidrix-Serpasil combination tablets than with Serpasil alone—and more rapid, too.

Esidrix-Serpasil controls complicating symptoms: With its calming action, the Serpasil component relieves anxiety that often accompanies hypertension. Serpasil also slows heart rate when tachycardia is present, while Esidrix promotes diuresis in edematous patients.

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SUPPLIED: Esidrix-Serpasil Combination Tablets, each containing 25 mg. of Esidrix and 0.1 mg. of Serpasil; bottles of 100.

REFERENCE: 1. Maronde, R. F.: Clinical report to CIBA.
ESIDEIX\*\*.M. (hydrochlorothiazide CIBA) SERPASIL® (reserpine CIBA)

## Esidrix-Serpasil®

A POTENTIATED ANTIHYPERTENSIVE

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THE COMPLETE RX FOR COUGH CONTROL

#### cough sedative / antihistamine / expectorant

- · relieves cough and associated symptoms
- in 15-20 minutes . effective for 6 hours or longer
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   rarely constipates
- · agreeably cherry-flavored

#### Each teaspoonful (5 cc.) of HYCOMINE contains:

6.5 mg.

12.5 mg. Ammonium Chloride 60 mg.

Supplied: As a pleasant-to-take syrup. May be habitforming. Federal law permits oral prescription.

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ABORATORIES Richmond Hill 18, New York

U.S. Pat. 2.630,400

DIAGNOSIS: Coronary Artery Disease

OBJECTIVE: Prolong Useful Life

METHOD OF CHOICE: Anticoagulant Therapy

DRUG OF CHOICE:

## THROMB

Because **ATHROMBIN** 

> begins more rapidly

"...initial prolongation of prothrombin time appears earlier than after other coumarin derivatives ... "!

"In our institution [University of Wisconsin Medical School] we start treatment with Warfarin sodium."2

"The great advantage... is that rapid and large changes in dosage can be quickly made, with the result that the correct maintenance dose can be rapidly determined."3

"Especially rewarding has been the prompt therapeutic response of acute thrombophlebitis to Athrombin therapy..."4

Because ATHROMBIN

> "controls" more simply, more reliably

"... a remarkably easy drug to control, as the response to a given dose can almost invariably be reliably predicted."3 "The ability... to provide long periods of stable levels of hypoprothrombinemia for any single patient makes it superior..."5 "In most patients, it is not difficult to arrive at a schedule in which prothrombin time determinations every two or three weeks are sufficient to maintain them with safety."2 "The action of Athrombin in maintenance dosage of 5 mg. daily has been so constant that I require prothrombin time estimations only once every two weeks."7

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offers safer. rapidly reversible anticoagulation

"... the [anticoagulant] effect ... can be rapidly reversed by vitamin K1. This property is very useful in the treatment of overdosage, particularly if there is bleeding."6 "... rarely causes excessive prothrombin depression

of a serious nature...produces no known systemic toxic effects."5

SUPPLY: Scored, 5 mg. tablets, light blue, in bottles of 50. Scored, 10 mg. tablets, white, in bottles of 50. Scored, 25 mg. tablets, yellow, in bottles of 25.

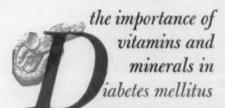
GITED REFERENCES: 1. Shapiro, S.: "Correspondence" in Brit. M. J. No. 4978:1301 (June 2) 1956. 2. Meyer, O. O.: Postgrad. Med. 24:110 (Aug.) 1958. 3. Toohey, M.: Brit. M. J. No. 5101:892 (Oct. 11) 1958. 4. Nodine, J.: Personal Communication, 1959. 5. Fremont, R. E., Jagendorf, B.: J.A.M.A. 165:1381 (Nov. 16) 1957. 6. Sine, H. S.: Practitioner 181:98 (July) 1958. 7. Dale, A.: Personal Communication, 1959.

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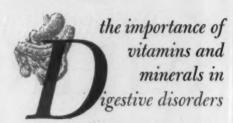
#### A RATIONALE FOR THERAPEUTIC VITAMIN-MINERAL

#### Subclinical vitamin-mineral deficiency in chronic degenerative disease

Most degenerative disease changes appear to be related to disturbances of cellular nutrition.¹ Subclinical vitamin or mineral deficiencies often occur despite an adequate caloric intake, and the consequent impairment of enzyme systems may injure body tissues.² Considerable evidence indicates that the vitamin reserve is frequently lowered to a serious degree in the older age groups most susceptible to degenerative disorders.³ Older persons also have increased requirements for such minerals as iron, iodine, copper, calcium and zinc.⁴.⁵.6



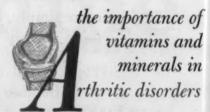
The diabetic has a higher requirement for the vitamin B-complex (especially nicotinic acid, thiamine, B<sub>12</sub>, and riboflavin) than the normal individual.<sup>7</sup> Great losses of calcium and potassium may occur during ketosis.<sup>7</sup> Low tissue zinc levels have recently been reported in a series of diabetic patients.<sup>8</sup> Metabolic deficiencies are frequently aggravated by diets which restrict or eliminate foods rich in essential co-factors.<sup>9</sup> Administration of more than normal requirements often produces a decided clinical improvement and may help to prevent neuropathic changes.<sup>7</sup>



Peptic ulcer diets are often deficient in essential vitamins. Symptoms attributable to B-vitamin deficiency are commonly observed in patients on such diets.<sup>10</sup>

Liver damage leads to faulty vitamin metabolism, and cirrhosis often produces severe vitamin deficiency.<sup>11, 12</sup> Pollack and Halpern recommend daily administration of therapeutic vitamins to patients with hepatitis or cirrhosis.<sup>11</sup> Large amounts of zinc are also lost by the cirrhotic patient.<sup>13</sup>

Great care must be exercised to avoid excessive depletion of vitamins and minerals in ulcerative colitis, regional enteritis, and chronic diarrhea. Patients with extensive bowel resections may require up to six times the normal daily vitamin requirement.<sup>14</sup>

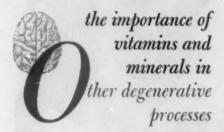


According to Spies, 15 nutritive failure is especially frequent in arthritic or rheumatic disorders. Some patients lose the desire to eat; some are too disabled to earn money to purchase required foods; still others are unable to perform all the necessary masticatory motions. Nausea and vomiting may prevent adequate absorption.

Therapeutic vitamins prevent or correct vitamin deficiency in the arthritic on an inadequate diet. In degenerative joint disease, vitamin therapy is recommended even when there is no demonstrable deficiency. Mineral supplementation may help prevent the depletion of calcium and potassium that occurs during therapy with cer-

#### LSUPPLEMENTATION

tain of the adrenal steroids. Iron<sup>17</sup> may be useful in preventing the anemia common in arthritis.



Vitamins and minerals appear to play a role in many other degenerative processes associated with aging. Studies by Wexberg, <sup>18</sup> Jolliffe<sup>19</sup> and others indicate that many of the symptoms attributed to senility or cerebral arteriosclerosis respond with remarkable speed to the administration of vitamins. Pyridoxine and nicotinic acid may even play an important role in the prevention of atherosclerosis.

Vitamin or mineral deficiency may be an unrecognized factor in still other situations. As Kampmeier states:

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease. Are there 'subclinical' degrees of vitamin deficiencies to search for, now that frank deficiency states have become so rare at least in the United States?"<sup>2</sup>

References: 1. Kountz, W. B.: Mod. Med. 25:102, Aug. 1, 1957. 2. Kampmeier, R. H.: Am. J. Med. 25:602, Nov. 1958. S. Overholer, W. and Fong, T. C. C. in Steglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264. 4. Kountz, W. B.: Indust. Med. 27:537, Oct. 1958. 5. Kountz, W. B. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 262. 6. Carlson, A. J. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 80. 7. Duncan, G. G.: Diseases of Metabolism, 4th edition, W. B. Saunders, Philadelphia, 1959, p. 812. 8. Griffith, G. and Hegde, B.: Illinois M. J. 115:12, Jan. 1959. 9. Pollack, H.: Am. J. Med. 25:673, Nov. 1958. 10. Sebrell, W. H.: Am. J. Med. 25:673, Nov. 1958. 11. Pollack, H. and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D.C., 1952, p. 57. 12. Kark, R. M. in Wohl, M. G. and Goodhart, R. S.: Modern Nutrition in Health and Disease, Lea and Febiger, Philadelphia, p. 615. 13. Vallee, B. L. in Harrison, T. R.: Principles of Internal Medicine, 3rd edition, McGraw-Hill, New York, 1958, p. 474. 14. Warthin, T. A. and Monroe, K. E.: M. Clin. North America Sept. 1958, p. 1419. 15. Spies, T. D.: J.A.M.A. 167:675, June 7, 1958. 16. Solomon, W. M. Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 627. 17. Ausman, D. C.: Journal Lancet 76:290, Oct. 1956. 18. Wesberg, E.: Am. J. Psychiat. 97:1406, 1941. 19. Jolliffe, N.: J.A.M.A. 117:1496, 1941.

help preserve tissue integrity and impede degenerative processes

## Theragran-M

Each THERAGRAN-M capsule-shaped tablet supplies:

Vitamin A . 25,000 U.S.P. units
Vitamin D . 1,000 U.S.P. units
Vitamin D . 1,000 U.S.P. units
Vitamin D . 1,000 U.S.P. units
Vitamin B . 1,000 U.S.P. units
Vitamin B . 10 mg.
Ascorbic Acid . 100 mg.
Ascorbic Acid . 200 mg.
Pyridoxine Hydrochloride . 5 mg.
Calcium Pantothenats . 20 mg.
Vitamin B . 20 mg.
Vitamin B . 20 mg.
Vitamin E . 5 Int. units
Calcium . 105 mg.
lodine . 0.15 mg.
lodine . 0.15 mg.
Potassium . 5 mg.
Copper . 1 mg.
Magnesium . 6 mg.
Magnesium . 6 mg.

Dosage: I tablet daily or as recommended.

Supply: Family Packs of 180.

Bottles of 30, 60, 100, and 1000.

Available with vitamins only as

#### **THERAGRAN**

SQUISS VITAMINS FOR THERAPY

Bottles of 30, 60, 100 and 1000 capsules and Family Packs of 180.

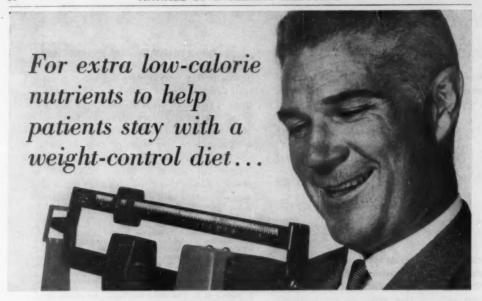
Also available: Theragran Liquid, bottles of 4 ounces; Theragran Junior, bottles of 30 and 100 capsules.

SQUIBB



Squibb Quality - the Priceless Ingredient

THERAGRAN . IS A SQUIRE TRADEMAR



#### New self-enriched Carnation Instant

25% more protein, calcium, B-vitamins, richer flavor than ordinary nonfat milk

Simple fatigue can discourage patients from staying with weight-control diet. A bonus of sustaining, low-calorie nutrients can help. Carnation Instant can provide such aid.

This new fresh flavor crystal-form nonfat milk can be self-enriched—to provide 25% more protein, calcium and B-vitamins than ordinary nonfat milk—and far richer flavor.

The patient simply adds 25% more crystals when mixing. Dissolves instantly in ice-cold water, ready to enjoy.

The chart below shows how this more delicious nonfat milk makes significant contributions, even to the *liberal* Recommended Daily Dietary Allowances of the National Research Council (1958 Revision).

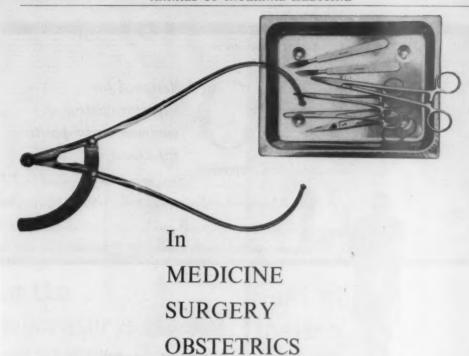
	Protein (Grams)	Calcium (Grams)	Riboflavin (Mg.)	Thiamine (Mg.)
NRC Allowances, Ages 25 to 65 Women	E000/8 102-02-0000	.8	1.8	1.6-1.3
Provided by 1 Qt. 25% self-enriched Carnation Instant	41.3	1.48	2.26	.40

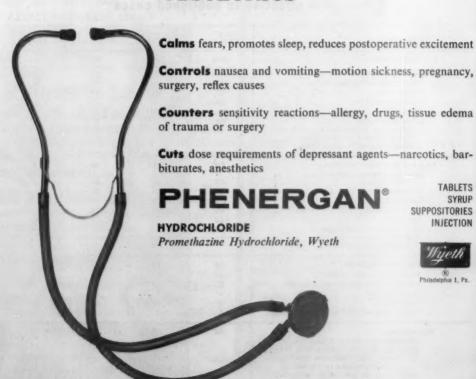
25% self-enriched Carnation Instant

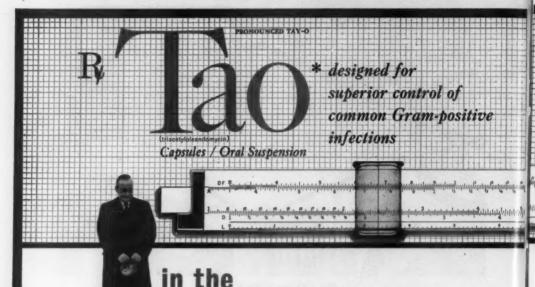
Simply add 1 tablespoon extra Carnation Instant per glass, or 1/3 cup extra Carnation Instant per quart, over regular package directions.











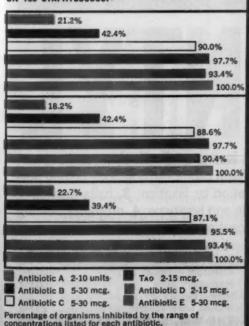
patient.						
95%	effective	in	published	cases1-8		

Conditions treated	No. of Patients	Cured	Improved	Failure
ALL INFECTIONS	558	440	80	30
Respiratory infections	258	206	31	19
Pharyngitis and/or tonsillitis	65	58	100 St. 100 St	200
Pneumonia .	90		17	7
Infectious asthma	44	38	THE PARTY OF	6
Otitis media	31	29	2	
Other respiratory (bronchitis, bronchiolitis, bronchiectasis, pneumonitis, laryngotracheitis, strep throat)	28		7	
Skin and soft tissue infections	230	101.00	38	1
Infected wounds, incisions and				
lacerations	41	33	105 (c.5	
Abscesses Furunculosis	51	43 51	700 ZAN (2013) (A	- T
Acne, pustular	58 43	28	6	1
Pyoderma Pyoderma	19	19	13	320 H EAL
Other skin and soft tissue	18	17	3137 612	<b>多数压力</b>
(Infected burns, cellulitis, impetigo, ulcers, others)	40	A WE		
Benitourinary Infections	28	10	3 3	8
Acute pyelitis and cystitis	10	<b>6</b> U.S.	2 6 6	
Urethritis with gonorrhea or cystitis	8			
Pyelonephritis	4			3
Salpingitis	5	· 10 事 11 第 1		3
Pelvic Inflammation with endometriosis	1			7
Miscellaneous	42	30		7 4 8
(adenitis, enteritis, enterocolitis, subacute bacterial endocarditis, fever, hematoma, staphylococcus carriers,				
osteomyelitis, tenosynovitis, septic arthritis, acute bursitis, periarthritis)				

# in the laboratory:

### over 90% effective against resistant staph

COMPARATIVE TESTS BY THREE METHODS (DISC, TUBE DILUTION, CYLINDER PLATE) ON 130 STAPHYLOGOGGI®



Other Tap advantages:

Rapidly absorbed - stable in gastric acid,? TAO needs no retarding protective coating

Low in toxicity – freedom from side effects in 96% of patients treated; cessation of therapy is rarely required

Highly palatable — "practically tasteless"? active ingredient in a pleasant cherry-flavored medium.

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children 8 months to 8 years, a daily dose of approximately 30 mg./Kg.body weight in divided doses has been found effective. Since TAO is therapeutically stable in gastric acid, it may be administered without regard to meals.

Supplied: TAO Capsules - 250 mg, and 125 mg, bottles of 60. TAO for Oral Suspension - 1.5 Gm., 125 mg, per teaspoonful (5 cc.) when reconstituted; unusually paldtable cherry flavor; 2 oz. bottle.

References: 1. Koch, R., and Asay, L. D.: J. Pediat. in press. 2. Leming, B. H., Jr., et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 3. Mellman, et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 4. Olansky, S., and McCormick, G. E., Ar. Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 5. Shubin, H., et al.: Antibiotics Annual 1957-1958, New York, N. Y., Medicai Encyclopedia, Inc., 1958, p. 679. 6. Isenberg, H., and Karelitz, S.; Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 13-17, 1958. 7. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy 5:527 (Aug.) 1958. 8. Kaplan, M. A., and Goldin, Ma. Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Truent, J. P. Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Truent, J. P. Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958.

#### Tao dosage forms— for specific clinical situations

Tao Pediatric Drops

For children-flavorful, easy to administer.

Supplied: When reconstituted, 100 mg. per cc. Special calibrated droppers—5 drops (approx. 25 mg.) and 10 drops (approx. 50 mg.).

TAO-AC (TAO analgesic, antihistaminic compound)

To eradicate pain and physical discomfort in respiratory disorders.

Supplied: In bottles of 36 capsules.

TAOMID\* (TAO with triple sulfas)

For dual control of Gram-positive and Gram-negative infections.

Supplied: Tablets, bottles of 60. Oral Suspension, bottles of 60 cc.

Intramuscular or Intravenous

For direct action - in clinical emergencies. Supplied: In 10 cc. vials.

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Science for the World's Well-Being



# KOLANTYL

Provides 4 necessary healing actions in one medication<sup>1</sup>...1. stops spasm—relieves pain; 2. neutralizes acid—with prompt-acting, long-lasting antacid combination free of constipation or laxation; 3. halts erosion—curbs necrotic effects of pepsin and lysozyme; 4. promotes healing—with soothing, protective coating on ulcerated area.

pleasanttasting, mintflavored KOLANTYL GEL Dosage: 1 tablespoonful gel, or 2 tablets, every three hours as needed. 1. Hufford, A. R.: Rev. of

1. Hufford, A. R.: Rev. of Gastroenterology 18:588.

Merrell

Formula: each tablet or 10 cc. gel contains — Bentyl (dicyclomine) hydrochloride . 5 mg. Aluminum hydroxide gel . . . . 400 mg. Magnesium oxide . . . . . . 200 mg. Methylcellulose . . . . . . . . . 100 mg.

Sodium lauryl sulfate . . . . . 25 mg.

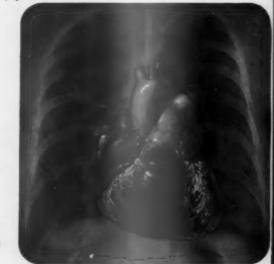
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DADEMARK HOLANTYL

"... safely, comfortably, and effectively useful in initial digitalization, redigitalization and maintenance digitalization of patients in

heart failure."



Rheumatic Heart Disease

# GITALIGIN

WIDEST SAFETY MARGIN-AVERAGE THERAPEUTIC DOSE ONLY 1/3 THE TOXIC DOSE.\$ FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

THESE SIMPLE DOSAGE EQUIVALENTS MAKE IT EASY TO SWITCH YOUR PATIENT TO GITALIGIN-0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.5 mg, digoxin or 0.1 mg, digitoxin.

#### Supplied:

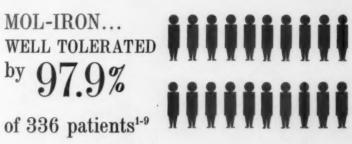
CITALIGIN 0.5 mg. Tablets-bottles of 30 and 100. GITALIGIN Injection Ampuls - 2.5 mg. in 5 cc. sterile, I.V. solution. GITALIGIN Drops 30 cc. bottle with special calibrated dropper.



WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

### FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

MOL-IRON... by 97.9%



But 22.4% G. I. side effects with FeSO.

VITAMIN C-"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid..."16

MOL- $\operatorname{IRON}$ 

WITH VITAMIN C TABLETS



Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. Polaramine — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. Polaramine offers swift, sure, safe action with these outstanding advantages — Therapeutically effective at lower dosages

• Therapeutically effective at lower dosages than other antihistamines • Highest therapeutic index of all antihistamines (3380)

• Fewer side effects than with other antihistamine preparations • Highly efficacious — a single Polaramine Repetable gives your patient all-day or all-night protection from discomfort of allergic symptoms

# POLARAMINE REPETABS

SUPPLY: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000 / POLARAMINE REPETABS, 4 mg., bottles of 100 and 1000 / Tablets, 2 mg., bottles of 100 and 1000 / Polaramine Syrup, 2 mg./5 cc., bottles of 16 cz. SCHERING CORPORATION «BLOOMFIELD.N.J.

symbol of the one-dose convenience you want for

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MAMINE Tale to Brand of Contro-chiotphenicamine meleste, REPETABS C Repent Action Tables

# SPONTIN°

#### A STATISTICAL REVIEW\* OF THREE HUNDRED THIRTY-THREE CASES

\*Records of Medical Department, Abbott Laboratories, North Chicago, Illinois

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories.

Its two components, and B, have been isola line state from the ferr of a new species of Nocardia lurida. Bot are active against gra teria and mycobacter mycete was isolated f ple collected from th Gods, Colorado Spi No other culture wh same antibiotic has

The chemical cha ristocetins are not co though they are known teric substances con phenolic groups a molecules with mo the vicinity of 4000 have good stability pH range of bloc SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the antil tericidal at th concentration hibits the gro also kills the

This obser for the majo lococci. Ho staphylococ have been to centration s minimum i produce a this reason SPONTIN

for the treat

and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to Spontin. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

tion, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or-SPONTIN is notably more ntly avail-

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of Spontin brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of Spontin has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

Summary and Conclusions

organisms holds true of staphystrains of cocci which uired a conher than the centration to ffect. It is for er dosage of

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estigators\* have recal response followration of SPONTIN dies have shown a ity on the part of ganism. Satisfactory may be expected m requires up to 25 ONTIN for inhibition llowing table shows sitivities of different e major pathogenic

pH range of blood SPONTIN is a lyophilized prepara-

safely control the "target symptoms" of emotional stress with the (0.25 mg. b.i.d.) of any neuroleptic\* agent



the promise of

# PBRMIT

in everyday office practice

# Primer on PERMITIL

#### . Why another psychopharmacologic agent?

The ever-expanding role of chemistry in the treatment of mental and emotional problems in this new era of psychopharmacologic drugs is amply attested to by the growing number of rauwolfia, mephenesin, diphenylmethane and phenothiazine derivatives now in clinical use. When one considers the wide range of indications to be treated—from severe psychosis to mild situational stress—it becomes somewhat clearer as to the reason for the number and diversity of drugs available. In addition, improvements and refinements of existing agents are constantly taking place. Drugs tailored to perform a selected, single function are emerging. So it is with Permitti.

#### Why another phenothiazine?

All members of this group contain a phenothiazine nucleus and a side chain attached to the nitrogen atom. Differences in potency are related to specific chemical alterations in these compounds. Clinical evidence demonstrates that the phenothiazines act principally, but to varying degrees, on several subcortical areas of the brain. Thus, certain of these drugs produce sedation and potentiate the action of barbiturates, while others do not; autonomic side effects (such as blurred vision, constipation) are produced by some and not by others; some have been shown to be very effective antiemetic agents. At certain dosage levels, the phenothiazine derivatives also may cause extrapyramidal side effects. These, however, are neuropharma cologic rather than toxic effects and are totally reversible.

Since there is a correlation between the dosage of a phenothiazine derivative and the frequency and the type of side effects it causes, the less of the drug needed to achieve therapeutic results, the less likely are serious side effects. Thus, the lower the effective dosage of a phenothiazine derivative, the lower the incidence of unwanted side reactions and, conversely, the higher the level of therapeutic response.

For these reasons, the search has been unceasing to develop a phenothiazine with an optimum therapeutic ratio.

#### What is a "neuroleptic" agent?

The term "neuroleptic" implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on specific subcortical areas which strongly influence emotional behavior in contradistinction to hypnotic agents which dull the senses. Neuroleptics achieve control of anxiety symptoms without inducing either somnolence or euphoria. Thus, there is an increase in the patient's capacity to cope with life's problems more successfully. The terms "tranquilizers" and "ataraxics" are descriptively impressive, but they fail to convey what seems pharmacologically unique.

#### . Why introduce the term "neuroleptic"?

A Because it has a precise psychopharmacologic meaning and is more descriptive of the action of Permittle than any other current term.

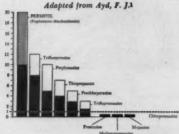
#### O. What is PERMITTEL?

A PERMITIL is a new anti-anxiety agent of extraordinary potency and effectiveness. Chemically, PERMITIL is 1-(2-hydroxyethyl)-4-[3-(2-triflu oromethyl-10-phenothiazinyl)-propyl]-piperazine dihydrochloride. The structural formula

#### Why is PERMITH unique?

Although PERMITIL can be broadly classified as a phenothiazine, it exhibits a spectrum of unique effects at unprecedented low dosage a feature that markedly distinguishes this compound from other anti-anxiety drugs.

### The Relative Therapeutic Potency of Various Phenothiazines



The potency of each drug was determined by the criteria proposed by Freyhan.<sup>3</sup> These were: (1) the attainable level of psychomotor inhibition, (2) the speed of action, and (3) the dosage required to obtain effective action.

### What are the distinctive clinical advantages of PERMITEL?

Extensive clinical studies have established important psychopharmacologic advantages for Permittle.

1. The effective dosage of Permitic (0.25 mg. b.i.d.) is the lowest safe dosage of any antianxiety agent. Since fractional milligram doses of Permitic usually produce a therapeutic effect, many of the annoying side effects of the other phenothiazines, which are doserelated, occur less frequently or not at all. In fact, any side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory. Permitic represents an advance over its predecessors because of its higher level of therapeutic response and low order of side reactions.

2. Unlike other phenothiazines, Permittl alleviates symptoms of anxiety, tension, agitation and emotional unrest without depressant effect, impaired alertness or slowed intellectual function. Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of Permittl. Thus, a significantly wider spectrum of "target symptoms" amenable to therapy is an outstanding property of Permittl.

 Onset of action is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

4. PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

#### Q. For what, specifically, is PERMITTE indicated?

PREMITIL is indicated for the control of the "target symptoms" of emotional stress so common in everyday office practice. The basic areas of usefulness for Premitical are: (1) behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states; (2) emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition; (3) chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

#### Q. Is the dosage schedule, as with many phenothiazine derivatives, complex and complicated?

No. PERMITIL has an inherently long duration of effect so that twice-a-day dosage provides the patient with day and night symptom alleviation. The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day. This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

### Q. What about side effects and contraindications to Permittl?

At the recommended dosage of Permitti, side effects have been observed infrequently or not at all. Permitti, as with other phenothiazines, is contraindicated in severely depressed states.

#### How is PERMITTL supplied?

PERMITIL is available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Ayd, F. J.: The current status of major tranquilizers, in press. 2. Freyhan, F. A.: Therapeutic implications of differential effects of new phenothiazine compounds, Am. J. Psychiat. 113:577-585 (Jan.), 1959.

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY



now...

quinidine b.i.d.

QUINAGLUTE® DURA-TAB S.M.

the only oral Sustained Medication\* quinidine gluconate, 5 gr.

for control of

# cardiac arrhythmias

 each dose of Quinaglute Dura-Tab S.M.\* maintains uniform plasma levels up to 12 hours.¹

(one dose every 12 hours)

- no night dosage needed.
- better absorbed and tolerated than quinidine sulfate.
- an unexcelled quinidine in premature contractions, auricular tachycardia, flutter, fibrillation.



Dosage: For conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days.

For maintenance 1 to 2 tablets every 10 to 12 hours.

Supplied: Bottles of 30, 100 and 250.

samples, reprint and detailed literature.

#### WYNN PHARMACAL

CORPORATION

5119 West Stiles Street Philadelphia 31, Pa.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

\*Patent Applied For

in Mexico.

it's called the 'turista' or 'Montezuma's revenge'



#### diarrhea by any name

GASTROENTERITIS
BACILLARY DYSENTERY
PARADYSENTERY
SALMONELLOSIS
DIARRHEA OF THE NEWBORN
NONSPECIFIC DIARRHEA
"SUMMER COMPLAINT"

usually responds rapidly to

# Cremomycin®

for rapid relief of all diarrheas-regardless of etiology

fruit-flavored, readily accepted by patients of all ages\*

Neomycin—rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as Shigella.

SULFASUXIDINE—an ideal adjunct to neomycin because it is highly effective against Shigella and certain other neomycin-resistant organisms.

Kaolin and Pectin—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

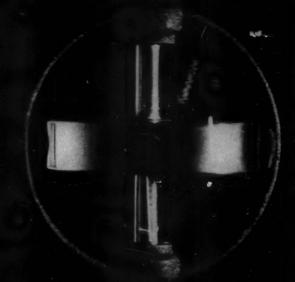
\*For infants, CREMOMYCIN may be administered in the regular bottle feeding, since its fine particles easily pass through a standard nursing nipple.



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CREMOMYOIN AND SULFASURIDINE ARE TRADEMARKS OF MERCK & CO.. IMC.

minimal disturbance of the patient's chemical and psychic balance...



still unsurpassed for <u>total</u> corticosteroid benefits

# Arls

Substantiated by published reports of leading clinicians:

• effective control
of allergic
and
inflammatory symptoms 1-20

minimal disturbance
 of the patient's
 chemical and psychic
 balance<sup>1,4,5,8-10</sup>

# Triamcinolone LEDERLE

At anti-inflammatory and antiallergic levels ARISTOCORT means:

- · freedom from salt and water retention
- · virtual freedom from potassium depletion
- · negligible calcium depletion
- · euphoria and depression rare
- · no voracious appetite no excessive weight gain
- · low incidence of peptic ulcer
- · low incidence of osteoporosis with compression fracture

Indications: rheumatoid arthritis; arthritis; respiratory allergies; allergic and inflammatory dermatoses; disseminated lupus erythematosus; nephrotic syndrome; lymphomas and leukemias.

Precautions: With ARISTOCORT all traditional precau-tions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms. After patients have been on steroids for prolonged periods, discontinuance must be carried out gradually.

Supplied: Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).

Diacetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

List of References 1-20 supplied on request.

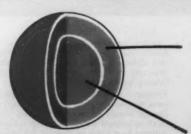


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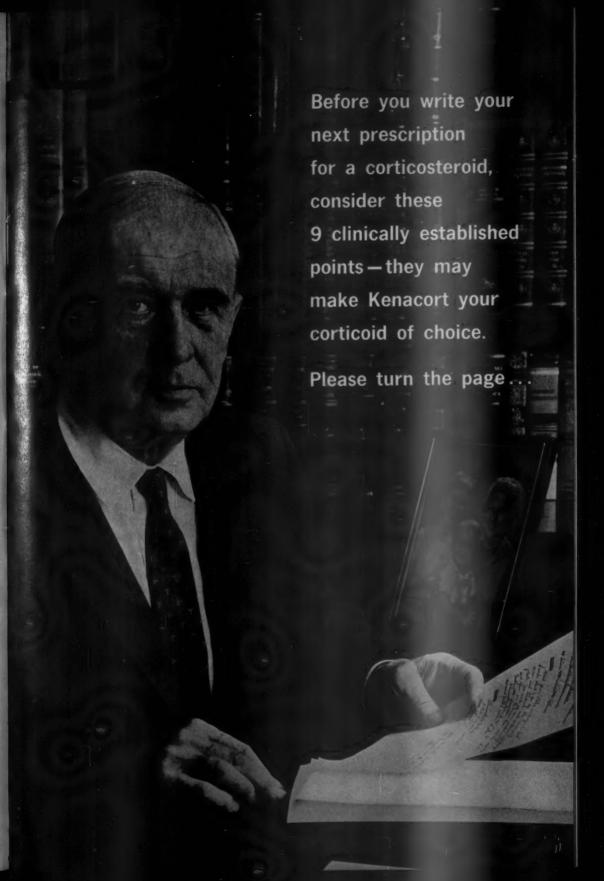
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Pancreatin, N.F	300	mg.
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initial therapy remarkably free from complications

Allison, J. R., Sr., and Allison, J. R., Jr.: Monographs on Therapy 3:99 (Oct.) 1958. pre-prescription point number 4

absence of edema

Council on Drugs: J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number 2

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-maintenance doses
are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J. A. H. A. <u>167</u>:58 (May 3) 1958. pre-prescription point number 5

less likely to create electrolyte disturbance

Bongievanni, A. M.; Mallman, W. J., and Eberlein, W. R.: J. Pediat. 53:3 (July) 1958.

pre-prescription point number 3

no sodium or water retention—low salt diet not necessary

> Hartung, E. F.: J. A. M. A. 167:973 (June 21) 1958.

pre-prescription point number 6

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

or blood pressure

Shelley, W. B.; Harus, J. S., and Pillsbury, D. M.;

J. A. M. A. 167-299 (June 21) 1999.

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Shelley, W. B.; Harun, J. S., and Pilisbury, D. M.: J. A. M. A. <u>167</u>:959 (June 21) 1958. Council en Drugs: J. A. M. A. <u>169</u>:257 (Jan. 17) 1959.

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J. A. M. A. 167:973 (June 21) 1958.



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BIBLIOGRAPHY: 1. Ehrlich, R.: Management of the Bowel after Hemorrhoidectomy with a Standardized Senna and Wetting Agent Preparation, Am. J. Surg. 95:826 (May) 1958. 2. Lamphier, T. A.: The Routine Postoperative Use of Standardized Senna With A Wetting Agent As A Bowel Evacuant, Am. J. Gastroenterol. 30:73 (July) 1958. 3. Yasuna, A. D., Halpern, A.: The Timed Integration of Stool Hydration and Peristaltic Stimulation In Constipation Correction, Am. J. Gastroenterol. 28:530 (Nov.) 1957.

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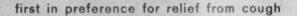
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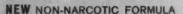
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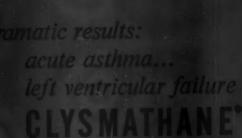
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References: 1. Ridolfo, A. S. and Köhistaedt, K. G. "A Simplified Method for the Roctal Instillation of Theophylline," Am. J. M. Sc., 237:585, May, 1939, 2. Ecochict, S. Personal Communications. X.

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Krantz, J. C., Jr.: The restless patient — A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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\*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

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Ensey, J. E.: Am. J. Obel. 77:155, 15

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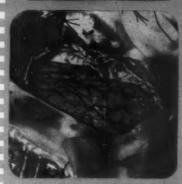
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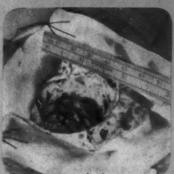
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#### TYPICAL PRESENTING SYMPTOMS

loss of normal drive inability to concentrate or work effectively indecisiveness irritability crying spells insomnia anorexia vague fears undue preoccupation with somatic complaints wide swings of mood generalized discomfort headaches dizziness palpitations hyperventilation epigastric distress

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REFERENCES: 1. Gearren, J.B.: Dis. Nerv. System 20:66 (Feb.) 1959. 2. Margolis, E.J.; Pauley, W.G.; Cauffman, W.J., and Gregg, P.C.: Scientific Exhibit at the 12th Clinical Meeting of the American Medical Association, Minneapolis, Minn., Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: ibid. 4. Ayd, F.J., Jr.: Clin. Med. 6:387 (Mar.) 1959.

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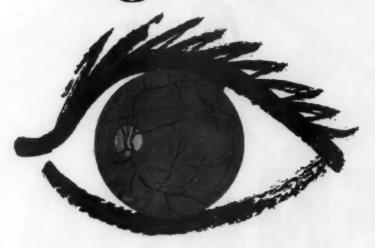


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References: 1. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: In press. 2. Winkelstein, A.: Am. J. Gastroenterol. 32.66 (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959.



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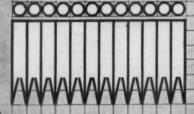
- 1. Boland, E. W., and Headley, N. E.: Paper read before the
- 1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
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### ANNALS OF INTERNAL MEDICINE

VOLUME 51

OCTOBER, 1959

NUMBER 4

#### CHANGING VIEWS ON HEART FAILURE\*

By JOHN McMichael, M.D., F.R.C.P., F.R.S., F.A.C.P. (Hon.), London, England

THE total picture of cardiac failure, with consequent dyspnea and edema as major manifestations, is one of considerable complexity. These clinical consequences are often given major attention in discussions of cardiac insufficiency, and at one time it was cynically remarked that the major offending organ in heart failure was the kidney. Certainly more attention was often paid to the kidney than to the central pump which is primarily involved.

Accurate methods of cardiac output determination put an end to many speculative hypotheses, and we can well remember the astonishment and incredulity with which the concept of "high output failure" was received. Where the organism required a high output, as in anoxic and anemic states, the overworked heart might go into failure. The simple switch of emphasis from output to work enabled us to appreciate that every failing heart is an overloaded heart. The overload may result from narrowed or incompetent valves, an elevated pressure head in the systemic or pulmonary arteries, or from inadequate muscle, either reduced in its anatomic bulk by ischemic scarring, or more subtly damaged by rheumatic inflammation. Excluded from the overwork definition we place only constrictive pericarditis, where the heart is hampered in its performance by enclosure in a rigid case—the armored or "Panzerherz" is the vivid German term.

All these factors will affect the heart at rest, but we are also compelled to consider what happens on exercise, when additional stimuli whip the heart to greater effort. When an individual becomes active in varying degrees the output of the heart is increased. The pump is driven at an increased rate, it ejects more blood at each beat, possibly responding to

<sup>\*</sup> Received for publication May 16, 1959.

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increased secretion of adrenalin. Sarnoff has recently shown that the response of the heart to any given venous filling pressure is set at a new high level by increased sympathetic nervous activity. All these mechanisms tend to supersede and obscure the simple working of Starling's law in normal animals and man. In the diseased or embarrassed heart, excessive tachycardia develops with relatively minor activity, but it is in the later stages that the heart loses its flexibility, the resting rate in failure with sinus rhythm settles round 90 to 100 per minute, and the heart ceases to respond to the other finely adjusted physiologic mechanisms. Just as the diseased kidney

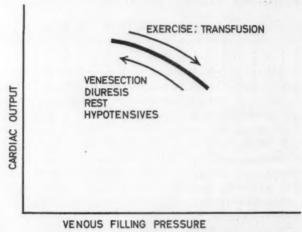


Fig. 1.

loses its range of concentrating power, so the heart loses its wide range of adaptation. It is at this stage that an elevated venous pressure may make its appearance, minor elevations being the rule at Grade III, becoming more extreme in Grade IV failure.

Starling demonstrated his law on the heart isolated from nervous and hormonal influences, and there are many grounds for accepting the working concept that some of his observations may apply to the heart in the more advanced stage of failure. He demonstrated a steadily rising cardiac output response as the venous filling pressure was elevated, but this response flattened out and a falling output reaction developed as the filling pressure was raised beyond a certain limit. It is this descending limb of the Starling curve which seems to correlate so closely with many observations in human heart failure.

The facts which have been demonstrated in man (figure 1) include the following:

- 1. Rapid transfusion in the anemic heart will precipitate failure.
- 2. Exercise will often elevate the venous pressure, but the output of the heart may actually fall (Hickam and Cargill, Howarth and Lowe). 1, 2
- 3. Venesection frequently increases the cardiac output.
- 4. Mercurial diuretics, by decreasing blood volume, lower the venous pressure and often increase the cardiac output.
- 5. Physical rest has the converse effect of exercise, dropping the venous pressure and increasing output.
- 6. The output of the heart in hypertensive failure will increase when venous pressure and arterial resistance are reduced by hypotensive drugs (Sobol et al., 1959).<sup>10</sup>

All of these points are probably fully appreciated, though I should like to reëmphasize the demonstration made by Pugh and Wyndham (1949) that mercurial diuresis was a potent method of reducing venous pressure, with corresponding hemodynamic improvement. The rapid loss of fluid by the kidney depletes the vascular fluid compartment quite substantially, and this constitutes an excellent method for maintaining an effect comparable to a venesection. It has taken a full generation since the introduction of mercurial diuretics to appreciate that they are more than mere symptomatic treatment for edema. Emphasis on the value of these drugs in reduction of blood volume is again being appreciated as we study the influence of chlorothiazide in enhancing the action of ganglion-blocking drugs in hypertension.

#### THE SIGNIFICANCE OF THE FALLING CURVE

We used to imagine that the falling part of the Starling curve was in some way related to overstretching of the myocardial fibers, realizing that this statement was incomplete and generally crude and noncommittal. The quick recovery which could take place during a venesection led us to think that the damage was in no sense irreparable, and that it certainly was more likely to be mechanical than due to any profound metabolic breakdown. A few clinical observations on tricuspid incompetence led us to the more systematic study of this phenomenon (McMichael and Shillingford, 1957).4 The pattern of tricuspid incompetence is readily recognizable on the jugular venous pulse, but more precisely in tracings within the right atrium. In gross instances of tricuspid incompetence, ventricular systole drives a large pulse wave into the jugular vein, but in a lesser degree it merely flattens out the normal X descent ("descent of the base"). In patients with ordinary forms of heart failure with systemic venous congestion (valvular, ischemic, hypertensive, cor pulmonale), Shillingford and Muller 9 found that tricuspid incompetence was recognizable in the right atrial tracing whenever the pressure in the right atrium reached 8 mm. Hg or 10 cm. water above the

zero point, the only exceptions being high output (anemic) states and constrictive pericarditis. Tricuspid incompetence is thus very common. It is even more important to recognize its variability from time to time, even in the same patient. Tricuspid incompetence is usually due to dilatation of the right ventricle and of the tricuspid valve ring. Inspiration, drawing more blood to the right ventricle, increases dilatation and therefore incompetence, while expiration may cause the characteristic pulse pattern and systolic murmur to diminish. Exercise will also exaggerate the condition, while rest may cause it to disappear. Venesection has been shown to diminish tricuspid incompetence, and physical rest does likewise.

When tricuspid incompetence is diminished or abolished by these and other measures, blood previously flowing backward at each systole may now go forward, and the effective cardiac output is thus increased. Sarnoff has observed that the development of the falling part of the Starling curve in the dog was frequently accompanied by incompetence of the atrioventricular valves. These observations seem to fit with our more recent experience in man. It is perhaps noteworthy too that calculations of cardiac work which depend only upon systemic blood flow may overlook the considerable expenditure of effort involved in driving back regurgitant streams of blood. In many gross cases of tricuspid incompetence the backflow through the tricuspid valve can actually exceed the forward flow.

A major part of our therapeutic effort in heart disease consists of attempts to remove the extra load imposed on the heart. In addition to such medical measures as digitalis, rest, diuretics and reduced sodium intake, the surgeon can come to our help in breaking adherent valves. Crude though his methods may be, they give promise of more profitable results as the technics for open heart surgery are improved. Nevertheless, the bulk of heart disease will long remain strictly in the realm of the physician.

Striking progress has been made in the treatment of the exacerbations of chronic bronchitis which can otherwise be lethal through their effects on the heart. Control by appropriate antibiotics and a skilled approach to the complicating asphyxia may lead to complete recovery of bronchogenic cor pulmonale. During the asphyxial episodes the pulmonary pressure rises and the right heart dilates. This whole process may be reversed by control of the infection and the consequent improved ventilation of the lungs.

In severe and malignant hypertension it is possible to prolong life by vigorous application of hypotensive drugs. When the heart is unloaded even by phasic and intermittent arterial blood pressure reduction, dilatation of the heart decreases, and often the electrocardiogram will show reversion towards normal.

The dynamics of early left ventricular strain are matters of great moment. One of the more interesting manifestations is the development of an auricular gallop sound. This sound is related to the end of inflow from the atrium into the ventricle, and its presence means that auricular filling is terminated:

the resulting sound is created either by distention of the ventricular wall or by an upward movement of the mitral valve cusps. Taking the load off of the left ventricle by the inhalation of amyl nitrite will cause a temporary regression of this sound. As the sound vanishes it actually moves closer to the first sound, until it becomes merged with it to reappear by "pulling out" as the pressure rises again. A similar migration of the sound may be seen following the injection of pentolinium or other ganglion-blocking drugs. Furthermore, the sound disappears even at the control (recumbent) blood pressure level following several weeks' use of the ganglion-blocking agents (Kincaid Smith and Barlow, 1959).\*

These phenomena, together with the appearance of an atrial sound, in ischemic heart disease indicate the importance of this physical sign in judging the imminence of more severe failure. A full appreciation of its mean-

ing will add greatly to our understanding.

The mode of action of digitalis is still perplexing. We know that it has no action in the normal or even in the hypertrophied heart that is measurable by our present clinical hemodynamic methods. Its action was most often demonstrable in left ventricular failure, particularly in hypertensive or ischemic heart disease. Sometimes one could see a marked increase in right ventricular pulse pressure following the administration of digoxin. On other occasions little seemed to happen. In still other instances, following improved function of a failing left ventricle which cleared engorgement of the lungs the right ventricular pulse pressure would fall. It is almost impossible to predict the metabolic state of the heart on which digitalis may exercise its action. Every time digitalis is given its administration is something of an experiment. When the experiment is successful the results are dramatically good; even when they are less striking, we cannot deny that the drug may have had some action outside the range of our present method of measurement. On still other occasions it may indeed have no beneficial action at all. So long as overdosage is avoided, however, it probably does no harm, and its continued administration to most cardiac patients is probably advisable (McMichael, 1959).5

Muller and Rorvik <sup>6</sup> have recently shown that during attacks of anginal pain the pulmonary vascular pressures are usually elevated. Relief of the angina by nitroglycerin is accompanied by corresponding relief of pulmonary hypertension. It is thus apparent that left ventricular failure is a common accompaniment of anginal pain. Whether the patient complains most of pain or of tightness in the chest or of shortness of breath may be largely a matter of his own subjective choice of words. It is always worth while finding out if shortness of breath is a component of the anginal discomfort. Where it is present, digitalis administration may be of value in reducing the

frequency of attacks.

I think we are making a little progress in our understanding of the behavior of the failing heart. Our efforts in treatment have become more

logical, and, best reward of all, our patients are being managed with greater achievement of comfort and well-being.

#### SUMMARIO IN INTERLINGUA

Con pauc exceptiones, disfallimento cardiac es le resultato de un carga excessive, absolute o relative, imponite super le corde. Le flexibilitate del corde normal es perdite. Es presentate datos que pare indicar que le corde human in disfallimento se comporta frequentemente como un preparato de Starling (i.e. un corde isolate ab omne influentia nervose o hormonal). Incompetentia tricuspidal explica multes del characteristicas de cordes in disfallimento, specialmente lor responsa a venesection. Potente diureticos reduce le volumine de sanguine e pote exercer un effecto simile a illo de venesection. Le elimination del causa del carga excessive—per exemplo le efficace tractamento de exacerbationes de chronic bronchitis o le reduction de un hypertension—resulta frequentemente in un marcate beneficio pro le patiente. A un certe sed pauco ben definite puncto in le disveloppamento de dysfunction metabolic in le myocardio, digitalis comencia devenir efficace. Le recognition, ab le puncto de vista clinic, del phase in que un responsa a digitalis pote esser expectate remane difficile a iste tempore.

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#### RESPONSIBILITIES OF THE INTERNIST IN OPEN **HEART SURGERY\***

By PAUL WINCHELL, M.D., Minneapolis, Minnesota

"I will follow that method of treatment which, according to my ability and judgment, I consider for the benefit of my patients and abstain from whatever is deleterious and mischievous." HIPPOCRATES

By tradition, the internist has concerned himself with the problems of diagnosis and medical treatment, and has sought the help of surgical colleagues when indicated. He has further devoted himself to the study of disease itself, and to the evaluation of treatment programs, whether they be medical or surgical. The functions of the internist relative to open heart surgery are exactly the same as for other areas of medicine.

Hippocrates' precept, simple and straightforward as it may seem, is difficult to follow in the specialized area of open heart surgery. The major difficulty is related to lack of knowledge about the natural history of the disease, the operative mortality, the immediate functional results of surgery, and the long-term consequences of the open heart procedures. This is not surprising in view of our relative lack of knowledge, until quite recently, of similar facets of the mitral stenosis problem. Before the internist can begin to cope with the more difficult problems just mentioned he must have a precise diagnosis, since his relationships with patient, family and surgeon depend, if they are to be meaningful, on a correct diagnosis.

Perhaps the greatest challenge and responsibility of the internist relate to the establishment of correct diagnoses. The variety of heart disorders now treated surgically by open heart technics is increasing steadily (table 1). Precision in diagnosis is of practical importance since, for example, the operative mortality and incidence of complications are about 2% for atrial defects of the secundum type, somewhat higher for the ostium primum syndrome, and somewhere between 15 and 50% for the atrioventricularis communis variety.1,9 Similarly, the presence of corrected transposition of the great vessels, although of no great physiologic significance, may make the proposed open heart operation impossible. Likewise, the relative importance of aortic stenosis or incompetence in a given patient alters the surgical approach and the expected results. For these reasons, the internist is obligated to seek out better diagnostic methods.

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Present improvements in diagnostic technics are of great interest. Retrograde aortography has proved to be safe and effective both in demonstrating the presence of aortic incompetence (figure 1) and in excluding it when suspected. In our experience, retrograde left ventriculography has been of much greater value in the evaluation of mitral incompetence than has direct left atrial puncture or indicator dilution studies using dyes, or radioisotopes (figure 2).

Isotope technics are proving especially useful in the localization of small left-to-right shunts that may be missed by the conventional multiple-site sampling technics and blood gasometric analysis. In this procedure the subject inhales a measured amount of radioactive methyl iodide, and samples of blood are withdrawn continuously from the right-sided heart chamber

#### TABLE 1

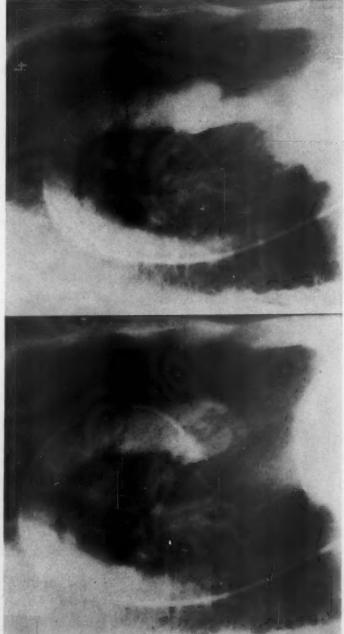
#### Lesions Now Treated by Open Heart Method

Ventricular septal defect
Atrial septal defect
Ostium primum syndrome
Atrioventricularis defect
Aortic pulmonic window
Aortic sinus aneurysms
Anomalous pulmonary venous return
Pulmonic stenosis
Pulmonic stenosis with ventricular septal defect
Mitral stenosis—reoperations
Mitral incompetence
Atrial tumors
Ventricular aneurysm
Aortic stenosis
Aortic incompetence

where the shunt is suspected. This same process is repeated from the chamber proximal to the first and the radioactivity of the samples is measured, giving a type of dilution curve in which isotopic iodine is the indicator (figure 3). The amounts of radioactivity are small—10 to  $12~\mu c$ —and the isotope is rapidly excreted. An indicator dilution curve can be done in the same way, but with samples taken from the femoral artery, and such curves have the same general significance as those done with dye indicators (figure 4.).

Direct puncture of the left ventricle is of great usefulness in measuring the intraventricular pressure and obtaining a systolic pressure gradient across the aortic valve by comparing the intraventricular tracing to a simultaneously recorded curve from a systemic artery (figure 5): Because it appears to be safer, retrograde catheterization of the left ventricle for the same purpose is preferable if it can be done.

These examples of diagnostic technics illustrate some of the newer methods that must be used in making correct diagnoses, an important aspect of the internist's responsibilities in open heart surgery. The future de-



The diastolic murmur Retrograde aortograms taken 1 second apart, showing marked reflux of contrast medium into the left ventricle. in this patient had been called a Graham Steell murmur. FIG. 1.

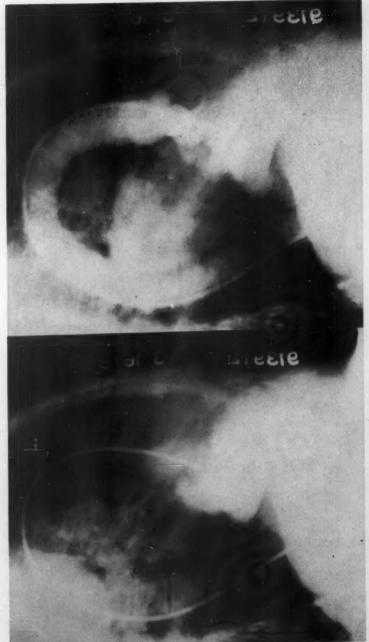


Fig. 2. Marked mitral regurgitation, demonstrated by retrograde left ventriculography. Films are I second apart.

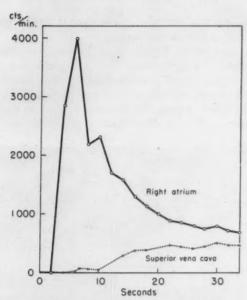


Fig. 3. Radioactive methyl iodide concentrations in right atrium and superior vena cava blood from a patient with a large atrial septal defect. The methyl iodide was given by inhalation.

velopment of even better diagnostic methods is another aspect of the same responsibility.

When a diagnosis has been made, it is possible to evaluate the risks and advantages of surgery in the light of the natural progression of the disease concerned. It is not possible to discuss at this time all of the open opera-

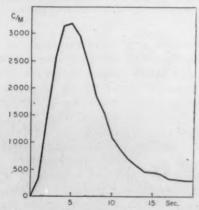


Fig. 4. Femoral artery blood content of radioactive methyl iodide given by inhalation.

tions in this way, but two examples will be useful: atrial septal defect of the secundum type, and calcific aortic stenosis.

The open repair of atrial defect is now quite well standardized, and the risk, in the absence of significant pulmonary hypertension, is 2% or less, one series of 57 consecutively operated cases without mortality having been reported.<sup>2</sup> Furthermore, enough patients have been studied postoperatively to know that the heart is probably returned to normal function, although the long-term effects of atriotomy are yet to be determined.<sup>2</sup>

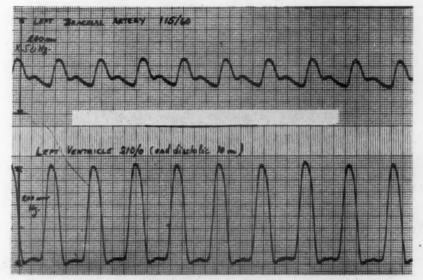


Fig. 5. Simultaneously recorded pressure curves from left ventricle and brachial artery in the presence of aortic stenosis. The systolic pressure gradient across the aortic valve is 95 mm. Hg.

It is of some importance that the natural course of atrial septal defect may be quite benign, and patients with it may live a comfortable life, attaining advanced age. The natural history of this disorder has been studied in considerable detail, and is likened to that of patent ductus arteriosus. About 95% of patients are doing well at age 20, 85% at age 30, 50% at age 40, and less than 25% at age 50. Clearly, not all patients with atrial septal defect are doomed to great morbidity and an early death. In making his decision about an individual case, the internist should keep these facts in mind. Furthermore, severe pulmonary hypertension is unusual as a complication of atrial septal defect, and subacute bacterial endocarditis is practically nonexistent—in marked contrast to ventricular septal defect. For these reasons, one can argue effectively against the routine closure of all atrial defects.

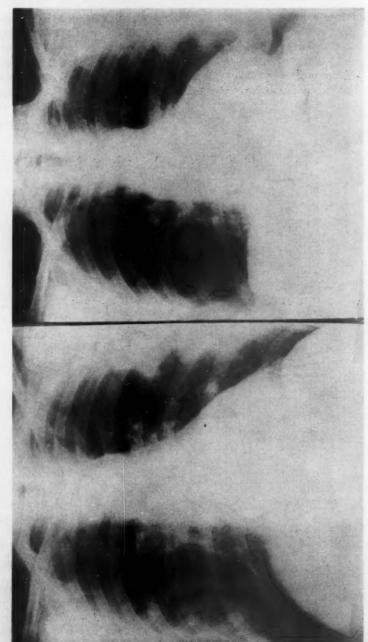


Fig. 6. Preoperative and postoperative chest x-rays from a patient with aortic stenosis. The stenosis had recurred when the second film was taken.

In contrast to atrial septal defect, calcific aortic stenosis, especially when symptomatic, carries a poor prognosis for function as well as survival. Survival data for symptomatic aortic stenosis are grim. In an older report, based on 123 autopsied cases, 67 were dead before age 50, and the final illness lasted, on the average, 4.3 months. Furthermore, 22% of the patients had experienced effort syncope, 19% had angina pectoris, and 15% had pulmonary edema.<sup>6</sup> In a more recent discussion it was stated that, of 52 patients with aortic stenosis who did not elect to have aortic valvotomy

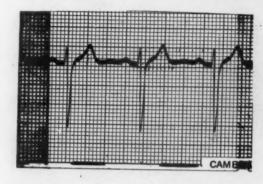




Fig. 7. Right bundle branch block developing after correction of tetralogy of Fallot.

done, 47 were dead within six months.<sup>7</sup> The indications for surgery in this disease are not uniformly agreed on, but in general it is felt that progressive disabling symptoms from aortic stenosis constitute a valid indication for considering operation.

The open operations for relieving aortic stenosis carry considerable mortality, just as does the untreated disease, and the long-term result of such procedures is not known. Simple aortic commissurotomy under direct vision is clearly not the answer. Figure 6 shows chest x-rays of one of the first patients to have open aortic valve surgery, in January, 1956. He was

somewhat improved for about one year, but since then has been markedly incapacitated by a recurrence of the aortic stenosis. Direct left ventricular pressure measurements at this time show a systolic pressure gradient of 95 mm. Hg across the aortic valve. His current x-rays show a considerable increase in left ventricular size since the operation.

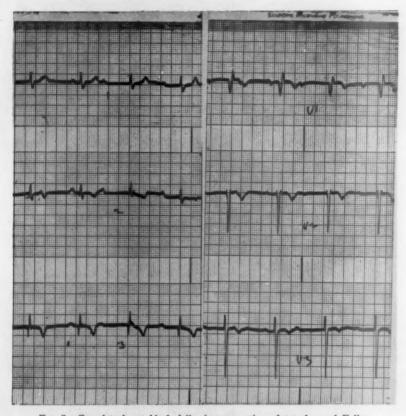
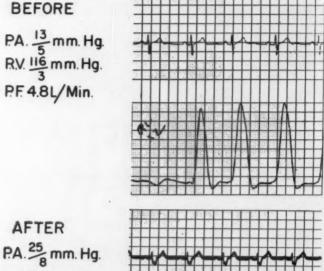


Fig. 8. Complete heart block following correction of tetralogy of Fallot.

Accurate estimates of operative mortality are not possible because of the limited number of patients submitted thus far to the operation. In one reported series, there was one operative death out of four patients operated on using the coronary artery retroperfusion technic, and the one patient in whom potassium citrate standstill was used also died—a mortality of two out of five cases. No objective data concerning long-term results in the survivors are given.<sup>8</sup> In another report on 24 patients with calcific aortic stenosis in whom open operations were done, the statement is made simply

that the results were "encouraging." No operative mortality or long-term result data were given.

In view of the marked deformity of valve tissues in calcific aortic stenosis, it is not likely that any simple attempt at remodeling those tissues will have any real usefulness. The problem will not be solved until a good



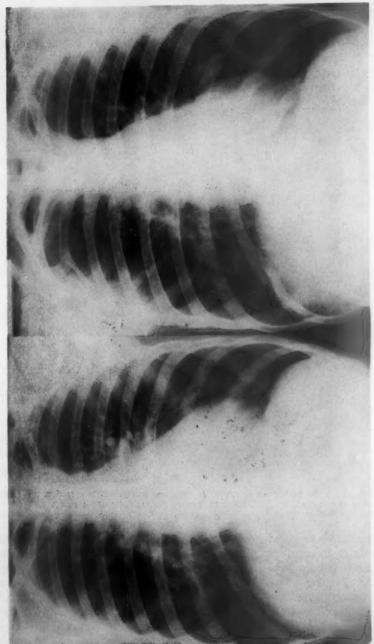
P.A. 25 mm. Hg.

R.V. 75 mm. Hg.

P. F. B.O L/Min.

Fig. 9. "Pull back" pressure tracings across the pulmonic valve. A definite systolic pressure gradient remains despite open resection of the pulmonic stenosis and use of an outflow tract patch.

prosthesis can be installed at the site of the aortic valve. The risk of bacterial endocarditis is still present with current surgical methods, and hence a recommendation for operative treatment of calcific aortic stenosis should be made only after careful consideration shows that there is no reasonable alternative.



Preoperative and postoperative chest views of a patient with a secundum atrial detect. Fig. 10.

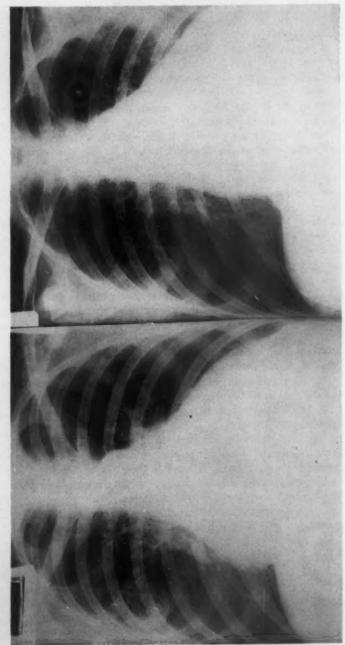
It is apparent, from the two examples given, that a rational decision for or against open heart surgery is very difficult. The same difficulties exist relative to all of the open heart operations, and this situation will continue until much more knowledge has been accumulated in this area.

Certain complications of open heart surgery do occur, and their management is in part a responsibility of the internist. Renal shutdown leading



Fig. 11. Same patient as in figure 10. At postoperative catheterization the catheter entered a pulmonary vein, probably after passing through the atrial defect that was not completely closed at operation.

to severe azotemia and even death has occurred in several instances. Infections in the cardiotomy itself and also empyema do occur. Traumatic pericarditis and myocarditis, very similar to the postcommissurotomy syndrome of mitral stenosis, also are seen. Of even greater seriousness are the conduction defects—simple bundle branch block (figure 7), and the often lethal complete heart block (figure 8). Recent advances in the treatment of surgically induced complete heart block, including isoproterenol-hydrochloride and particularly the external pacemaker attached to an elec-



Preoperative and postoperative chest views of a patient submitted to resection of the noncoronary aortic valve cusp. The aortic valve is now bicuspid. F1G. 12.

trode embedded in the myocardium, have markedly reduced the mortality from this unfortunate complication.

One additional responsibility of the internist is to participate in the evaluation of surgical results. Experience with mitral valvotomy, for instance, has shown that objective measurements are necessary for proper evaluation. Subjective patient responses are often misleading. Many questions remain unanswered, such as the long-term effect of cardiotomy on heart function, the ultimate effect of complete heart block in those patients who survive with this complication, the eventual fate of plastic substances used in outflow tract patches and in valvular repairs, and the incidence of bacterial endocarditis following surgical treatment of heart defects.

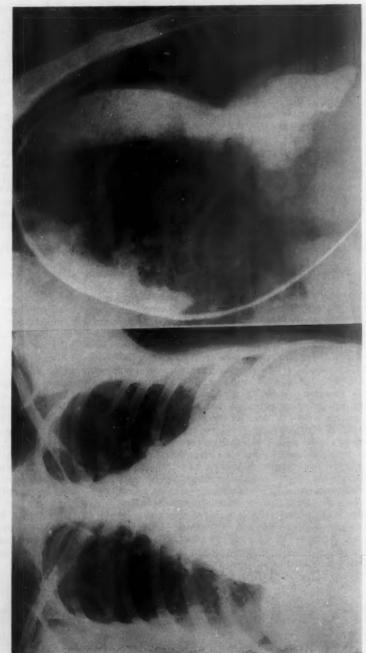
Although most open operations are theoretically curative, in actual practice this is not always true. Figure 9 shows the pressure curves in the pulmonary artery and right ventricle, both before and after open correction of tetralogy of Fallot. A significant pressure gradient persists across the pulmonary valve. Figures 10 and 11 show persistence of an anomalous pulmonary vein, and probably of the atrial defect as well, in a patient previously operated on by the open method. The total pulmonary blood flow in this patient is lower than before surgery, indicating at least partial closure of the atrial defect.

A final evaluation of several new operations must await the further passage of time. Figure 12 shows the preoperative and postoperative chest x-rays of a patient who has had the noncoronary cusp of the aortic valve removed. His was an unusual instance of fenestration of the noncoronary cusp as a consequence of bacterial endocarditis. Following surgery, the systemic arterial diastolic pressure has come up to a normal level, but the heart remains large, a distinct, but lesser, aortic diastolic blowing murmur persists, and the patient has experienced several episodes of supraventricular tachycardia. The ultimate fate of the now bicuspid aortic valve in this patient is not known.

Finally, figure 13 shows the left ventriculogram made in a young woman after open plastic repair of an incompetent mitral valve. The previously marked systolic murmur is much reduced in loudness, and now an opening snap and a diastolic rumble are heard at the cardiac apex, the patient continues to have atrial fibrillation despite attempts to convert it to a sinus rhythm, and her functional capacity has changed only from class III to class II. This woman would seem still to have serious heart disease.

#### SUMMARY

The primary responsibility of the internist in the area of open heart surgery is to give his patient the best advice possible. To exercise this major responsibility, a precise diagnosis must be made, and in order that diagnoses may be accurate, new and improved diagnostic methods are essential. In addition, the internist has responsibilities in the treatment of



Chest film and retrograde left ventriculogram following open correction of mitral incompetence. Minimal valvular incompetence remains. 13. Fig.

surgical complications and in the evaluation of immediate and long-term results of open heart operation.

#### SUMMARIO IN INTERLINGUA

Le prime responsabilitate del internista con respecto a operationes cardiac aperte es consiliar le patiente le plus intelligentemente possibile. Pro isto, un accurate diagnose debe esser establite, e pro obtener un ver accuratia diagnostic, moderne e meliorate methodos de examination es indispensabile. In plus, le internista ha responsabilitates in le tractamento de complicationes chirurgic e in le evalutation del resultatos a breve e a longe vista.

Le major difficultate in satisfacer iste responsabilitates es relationate al inadequatia de nostre cognoscentias del morbo, del mortalitate operatori, del immediate resultatos functional del operation, e del consequentias a longe vista del technica de operation a corde aperte.

Le chirurgos trova minus difficile completar lor labor a bon successo si un precise diagnose es disponibile. Ergo, grande attention in le effectuation e le interpretation del tests diagnostic es requirite. Es etiam un obligation del internista cercar e discoperir melior methodos diagnostic. Meliorationes currentemente disponibile in le technica diagnostic es:

- 1. Aortographia retrograde, usate pro demonstrar le presentia de incompetentia aortic.
- 2. Retrograde ventriculographia sinistre, usate in le evalutation de incompetentia mitral.
  - 3. Technicas a isotopos, utile in le localisation de micre shunts sinistro-dextere.
- 4. Punctura directe del ventriculo sinistre, usate in mesurar le tension intraventricular e in determinar le gradiente de tension systolic trans le valvula aortic per comparar le registration intraventricular con le simultaneemente registrate curva ab un arteria del circulation systemic. Catheterismo retrograde del ventriculo sinistre es un technica plus salve e debe esser preferite si illo es practicabile.

In adultos, le plus simple e le plus generalmente disponibile operation a thorace aperte es le reparo de defectos atrio-septal, characterisate per un risco operatori pro defectos de foramine oval de 2% o minus. Le numero de patientes assi operate es sufficientemente grande pro que nos pote asserer que le resultante melioration functional es considerabile. In le majoritate del casos le patiente deveni functionalmente normal. Per contrasto con isto, le risco in reparos aperte de stenosis o incompetentia aortic amonta a quasi 50%, e le fato del superviventes non es cognoscite.

Certe complicationes de chirurgia a corde aperte remane un possibilitate, e quando tales occurre, lor manipulation es in parte un responsabilitate del internista. A parte le usual complicationes de thoracotomia, complicationes specific es bloco cardiac complete, disfallimento renal, pericarditis e myocarditis traumatic, e—como occurrentia exceptional—vulneration cerebral in consequentia de embolo o hypoxia.

Studios postoperatori es necessari pro mesurar le grado de melioration e le importantia del morbo residue ancora presente. Le patiente in convalescentia debe viver intra le limites establite per su symptomas. Ille debe esser tenite sub observation de maniera que possibile complicationes tardive pote esser attaccate si tosto que illos se manifesta e de maniera que le progresso del patiente pote esser studiate.

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## THE MANAGEMENT OF ABNORMAL BLEEDING FOLLOWING EXTRACORPOREAL CIRCULATION\*†

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In the early days of the development of artificial heart-lung machines, abnormal postoperative bleeding was a very frequent phenomenon, and an unmanageable hemorrhagic diathesis is an occasional obstacle to newcomers in this field. Some of the well established groups with hundreds of human cases to their credit claim that they no longer see an abnormal postoperative bleeding tendency. Undoubtedly they have succeeded in empirically establishing a successful routine, and are careful not to vary from it even to a minor degree without carefully checking the effect. Other teams, believing that they are copying the leaders in complete detail, are not always successful, presumably because of minor variations in technic.

Our group has devoted considerable attention to the effect of various extracorporeal technics on the blood coagulation system in an effort to explain the causes of abnormal bleeding and thus to derive a successful program of prevention and management. Our own experiences and those reported by others indicate that the hematologic effects of heart-lung bypass may vary greatly from one group to the next, and even, in the same group with the same general technic, from one operation to the next. Nonetheless, the approach to be outlined should indicate the source of trouble in any given case and thus permit its correction. We have never had any abnormal postoperative bleeding which we were unable to control.

It should be recognized at the outset that strict hematologic controls are not necessary for every operation. A successful team with a technic that works well can rightly expect no abnormal hemorrhage following a short, atraumatic bypass. (We shall explain what we mean by "short" and "traumatic" later.) Such operations, then, will call for none of the tests to be described.

Table 1 outlines the various coagulation abnormalities that have been shown to result from heart-lung bypass.

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#### TABLE 1

Coagulation Abnormalities That May Result from Extracorporeal Circulation

- I. Thrombocytopenia II. Improper heparin neutralization
- III. Loss of plasma coagulation factors
  - A. Fibrinogen
    - 1. Fibrinolysis
  - B. Intravascular coagulation
  - C. Direct denaturation

#### PLATELETS

Blood platelet counts drop during the period of extracorporeal bypass.<sup>1</sup> This decrease has always been found in our experiences with a wide variety of bubble, film and membrane oxygenators. Platelet disappearance is due to removal from the circulation by the patient of platelets which have been damaged. Some of these are donor platelets which have lost viability prior to, as well as during, use in the machine. (An exchange transfusion takes place during the bypass.) Others are patient platelets which have been damaged during passage through the artificial external circulation. Platelet counts rarely dropped below 90,000 per cubic millimeter in our first 125 operations. Most of the loss occurs in the first few minutes, but there is a slow, steady fall as long as the bypass continues (table 2), and with perfusions lasting many hours, significant thrombocytopenia may occur. In general, the platelet count returns to safe levels shortly after the bypass. Abnormal bleeding due to thrombocytopenia should not be seen, therefore, unless other factors are added to depress the platelet count further. Two such factors have been recognized: dirty equipment, and excessive transfusion of blood with nonviable platelets.

In the dog laboratory we have seen extreme thrombocytopenia with bleeding in two short series of experiments. On one occasion, several consecutive operations were associated with a severe drop in the platelet count before the bypass began. The fault was a dirty blood pressure recording catheter.2 Almost complete loss of platelets during bypass occurred with our first experimental membrane oxygenator, which was tested for leaks by being allowed to stand full of sterile saline for several days. Thrombo-

TABLE 2 Mean Platelet Fall During Period of Extracorporeal Circulation

293,000 per cu. mm.
199,000 per cu. mm.
205,000 per cu. mm.
206,000 per cu. mm.
157,000 per cu. mm.
175,000 per cu. mm.
140,000 per cu. mm.

(Five Experiments)

(There is some variability, probably due to inadequate mixing of donor and patient blood.)

cytopenia no longer occurred when Zephiran was added to the saline. We believe these episodes were caused by the development of pyrogens (endotoxins) in dirty equipment. Cleanliness is as important as sterility in these experiments. Equipment which will be reëmployed should be thoroughly cleaned immediately after use and sterilized at once. Once pyrogens have formed they are almost impossible to remove.

Bleeding from thrombocytopenia is recognized as resulting from the transfusion of excessive amounts of blood containing nonviable platelets.<sup>8</sup> All of the blood we use for our operations is less than 24 hours old, and is in either plastic bags or siliconed bottles. There is probably some platelet survival from this donor blood, for in all of our cases where 20 or fewer units have been used on the day of operation, the platelet count has returned rapidly to normal following the bypass and has stayed there. However, in the two cases where unusual surgical considerations dictated the use of more than 20 units, the platelet counts fell again to levels usually associated with bleeding. In one of these cases, at least, the count remained at that level for five days and then rapidly rose.<sup>2</sup> The prolonged period of thrombocytopenia suggests that the patient's platelet reserves had been completely exhausted.<sup>4</sup>

A platelet count should be done, then, if a patient continues to bleed abnormally following an operation with an artificial heart-lung machine. If abnormal bleeding persists and the count remains below 60,000 per cubic millimeter, steroids may be of some help. The case mentioned above, whose platelet count remained at 50,000 for five days, was given steroids and had no abnormal bleeding. Persistent low platelet counts are also an indication that all subsequent blood replacement should be with absolutely fresh blood in plastic bags or siliconed bottles. Platelet concentrates may be used, if necessary. It should be emphasized, however, that thrombocytopenia which persists for only an hour or two following bypass needs none of these special measures. The platelet count will usually return to normal before the rate of blood loss through the chest drainage tube slows.

#### HEPARIN NEUTRALIZATION

Obviously, if sufficient heparin is not used, blood may clot in the extracorporeal circulation. Equally true, but less generally known, is the fact that if only a borderline amount of heparin is employed, coagulation may occur to the point of depositing fibrin on the foreign surfaces in a layer too thin to be seen. This "intravascular" coagulation can proceed to the point of depleting the blood of essential clotting factors, and thus lead to the production of a hemorrhagic state. Too little heparin is thus definitely dangerous. On the other hand, there is no evidence that larger amounts will lead to more of a tendency to bleed than barely adequate amounts, and large concentrations are just as easy to neutralize as small ones. Complete prevention of coagulation seems to occur if the patient is given 3,000 units of heparin per kilogram, and if the donor blood is collected with 25,000 units per 500 ml.

Following the heart-lung bypass, if heparin is not properly neutralized, blood loss will be considerably greater and more prolonged. Most successful groups have empirically arrived at a dose and method of administration of protamine that work for them. Some give it in a single dose, others by slow intravenous drip.

With the development of less traumatic pump-oxygenators, we no longer see the drop in the blood pressure we used to see if too much protamine was given too fast.<sup>5</sup> (This hypotension was an index of how much damage was done to the blood.) The required amount of protamine thus can be given in a single injection to limit unnecessary blood loss. We find it most convenient to inject it into the tubing of a blood transfusion set and let it run in over a period of several minutes. We have never seen "heparin rebound," <sup>6</sup> and do not believe that it exists unless the heparin has been injected into the tissues to form a depot, instead of intravenously.

Since a drop in the blood pressure with protamine is no longer seen, there is no need to be so concerned about giving the minimally effective dose of protamine. There is a fairly wide margin of safety between this minimally effective dose and an amount large enough to prolong the blood clotting time. It is this wide margin that permits the use of a standard dose of

protamine following most operations.

postoperative hemorrhage.

However, the dose required, as measured by our simple protamine titration technic, will vary with the type of pump-oxygenator and other differences in technic. The ratio between the minimal effective dose of protamine and the amount of heparin given has varied from 0.5:1 to 1.5:1. We feel safer in measuring the required dose by the titration technic whenever our technics have varied, the bypass has been unusually long and traumatic, or there is any special reason to be concerned about the possibility of

The method, in brief, consists of adding 1 ml. of blood (usually taken from the oxygenator just before it is shut off) to each of a row of tubes, each of which contains protamine in 0.1 ml. of saline (from 0 to 50 mcg. of protamine at 5 mcg. increments). At the end of 15 minutes the tubes are tilted. The one with the smallest amount of protamine which has clotted indicates the minimal effective dose of protamine per milliliter of blood. Experience has taught us that heparin and protamine are probably distributed to some extent extravascularly, for we find that the dose of protamine for the patient must be calculated by multiplying the requirement per milliliter by a volume equal to 100 ml. per kilogram of body weight, a figure considerably higher than is usually given for the blood volume. In an occasional case, even this dose will be a bit short.<sup>2</sup>

Subsequent titrations, if neutralization is in doubt, need be done with only the first four or five tubes (0 to 15 or 20 mcg.), since the endpoint

should be quite close to zero. If the heparin in the patient is properly neutralized, all tubes should clot simultaneously. If excessive amounts of protamine have been given, the zero tube will clot before the others. If all tubes clot simultaneously, but take longer than 15 minutes, a clotting defect is present which is not due to an excess of either heparin or protamine (table 3).

Table 3
Clotting Times in Protamine Titration Tubes Under Varying Conditions

Protamine concentration (µg. per ml. blood)	., 0	5	10	15
1. Heparin properly neutralized	10'	10'	10'	10'
2. Insufficient protamine	25'	10'	10'	10'
3. Excessive protamine	20'	22'	25'	30'
4. Other clotting defect	25'	25'	25'	25'

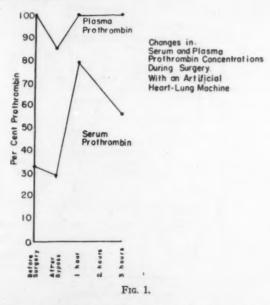
#### FIBRINGEN AND FIBRINGLYSIS

Severe loss of fibrinogen occurred with the traumatic early experimental pump-oxygenators; 8 however, hypofibrinogenemia no longer seems to be a problem in our own experience 2 and that published by others. On the other hand, fibrinolysis has been reported as a cause of abnormal bleeding following extracorporeal circulation.9 We have never had such an experience, but we presume that our failure to observe it merely indicates how variable the results are under different conditions. It is our practice to leave our protamine titration tubes at room temperature for 24 hours so that they may be observed for clot lysis. Lysis was observed on one occasion only, and this patient had had no abnormal postoperative bleeding. The clinical significance of fibrinolysin, demonstrated by more sensitive technics than simple observation of whole clotted blood, is somewhat debatable; and such tests are probably unnecessary as a routine procedure in the practical management of these cases. However, fibrinolysis unquestionably does occur on occasions as a complication of major surgery, and surgery in the chest has been implicated numerous times.10 Therefore, one must remain alert to this possibility. If abnormal bleeding occurs postoperatively associated with clot lysis, the administration of steroids may be tried.10 Considerable investigation is under way to develop useful inhibitors of fibrinolysin or its activators. One such substance which appears to be promising is epsilon aminocaproic acid.11 If fibrinogen is low (as demonstrated by a poor clot when thrombin is added to the blood),12 fibringen should be infused.

#### OTHER PLASMA COAGULATION FACTORS

Our experience in several hundred human cases has been confined to two types of film oxygenators, the Osborn disposable plastic bag type <sup>18</sup> and the Melrose rotating cylinder; <sup>14</sup> however, it seems reasonable to believe the remarks made are equally applicable to any machine in current use. Following the average perfusion, there are no detectable changes in plasma

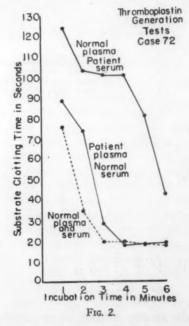
coagulation factors. If the bypass lasts 30 minutes to an hour, minor changes may be detectable by sensitive tests, but without obvious clinical concomitants. Bypasses over two hours in duration may produce marked changes associated with abnormal postoperative bleeding. The major factor in the production of this change in blood coagulation factors appears to be the suction of blood from the interior of the heart. Generally speaking, a large amount of coronary return means greater abnormalities. However, a really large return, so large that a continuous flow of blood moves up the suction tube, appears to cause less damage than if there are frequent breaks in the column of blood.



The coagulation abnormality induced occurs in two phases. Changes due to phase one can be detected first on blood removed from the machine at the end of a bypass. The tubes which clot in the protamine titration coagulate with unusual rapidity, certainly in less than five minutes. If prothrombin consumption is determined on tubes in which the heparin is completely neutralized, but protamine is not present in marked excess (less than 25 mcg. excess per milliliter of blood), the prothrombin utilization will be found to be normal or excessively good. The short clotting time and the rapid prothrombin consumption suggest that thromboplastic materials have been liberated into the plasma, probably from trauma to the blood cells. This first phase lasts only minutes.

After the usual neutralizing dose of protamine has been given, the patient will continue to ooze to an abnormal degree. Recheck of the protamine

titration will demonstrate that all of the tubes clot simultaneously but the clotting time is *prolonged* to a variable degree. The second phase of the reaction is now present. Prothrombin consumption at this point is markedly impaired (figure 1), implying a defect in the first stage of coagulation. Second-stage defects are less likely to occur and are of lesser degree. We believe that this defect may be responsible for some of the situations which have been blamed on "heparin rebound." In every case where the first stage defect has been investigated, the defect has been shown to be a deficiency of a factor present in normal serum, presumably plasma thrombo-



plastin component (PTC) (figure 2). Since this deficiency cannot be explained by intravascular coagulation, it seems most reasonable to ascribe it to direct denaturation of the protein in the external circuit. It should be pointed out, however, that O'Brien 15 has demonstrated an apparent transitory PTC deficiency following simple administration of heparin.

The most important single thing to remember about this defect is that it is spontaneously reversible. In every case we have followed, the results of tests have improved rapidly in the four to five hours following the operation. Since relatively little fresh blood was being administered during this period, the improvement was presumably due to replacement of the missing factors by the patient. No therapy is required, therefore, except to replace the blood as it is lost through the chest drainage tube, preferably with fresh

blood in plastic bags or siliconed bottles. The laboratory tests will return to normal before the abnormal bleeding slows.

The chief thing to avoid is superimposing upon this temporary defect a more serious one. Two mistakes can cause this: First, if a protamine titration technic is not being used, the abnormal loss of blood and the prolonged clotting time may lead to administration of additional amounts of protamine to the point where excess protamine exerts an anticoagulant effect. Second, the use of too many bottles of routine bank blood, with its non-viable platelets, can result in the hemorrhagic syndrome due to the thrombocytopenia of massive blood replacement.

#### TABLE 4

#### Recommended Coagulation Studies

- I. Before operation:

  - A. Check history for bleeding tendency.
    1. Do special studies only if indicated.
    B. Note clotting time of blood sample drawn for cross-matching.
  - C. Check blood platelets on smear.
- II. After operation (if bleeding state is present):
  - A. Platelet count.
  - B. Protamine titration.
    - 1. Is heparin properly neutralized?

    - 2. Is the clotting time normal?
      3. Is a good firm clot produced?

#### RECOMMENDED PROCEDURE (TABLE 4)

At the time the patient is given an appointment for operation, he is questioned as to previous history of abnormal bleeding. If the history is at all suggestive, any laboratory tests necessary to rule out a coagulation defect are performed. A true bleeding diathesis, such as hemophilia or thrombocytopenic purpura, would be a contraindication to operation, even though the exchange transfusion with fresh blood that results from the heart-lung bypass might temporarily correct the defect.

A blood sample is drawn at the time of the first visit to determine the patient's blood type. Observation of the time it takes this blood to clot will provide additional information as to the possible presence of a coagulation defect. Extreme care is taken to ensure that all blood used during the procedure is compatible. Each unit should be compatible with every other unit, as we'll as with the blood of the patient. Administration of incompatible blood can itself produce a bleeding syndrome.16

If there is no evidence to suggest a hemorrhagic diathesis, simple inspection of the blood smear at the time of admission to the hospital is enough to rule out thrombocytopenia of any consequence.

If abnormal bleeding occurs following operation with a heart-lung machine, a protamine titration and a platelet count are done. Any abnormalities uncovered are managed according to principles already outlined. If the results of the titration test indicate a normal clotting time, proper heparin neutralization, and a good firm clot—if there is an adequate platelet count—and if, despite this, bleeding persists to a grossly unusual degree, the patient should be reëxplored with the expectation of finding one or more bleeding points that need ligation.

#### SUMMARY

Although the improvement in artificial heart-lung machines has made abnormal postoperative bleeding unusual, a hemorrhagic state may still occur under a variety of circumstances. Severe thrombocytopenia may be induced by the use of improperly cleaned equipment, or by the administration of excessive amounts of bank blood with nonviable platelets. Inadequate neutralization of heparin or (in rare instances) administration of excessive amounts of protamine may result in a hemorrhagic state. Fibrinolysis has not occurred in our series of over 125 cases, but remains a possibility. Unusually long and traumatic bypasses may result in depletion of some coagulation factors, with involvement particularly of the first stage of coagulation. The defect is spontaneously self-limited. Methods to avoid these troubles and to manage them, if they nonetheless occur, have been outlined.

#### SUMMARIO IN INTERLINGUA

Ben que le melioration technic del machinas corde-pulmon artificial ha facite anormal sanguination postoperatori un occurrentia inusual, le advento de un stato hemorrhagic remane un possibilitate sub varie circumstantias. Grados sever de thrombocytopenia pote esser inducite per le uso de inadequatemente detergite componentes del apparatura o per le administration de excessive quantitates de sanguine de banca con non-viabile plachettas. Le imperfecte neutralisation de heparina o (in casos rar) le administration de excessive quantitates de protamina pote resultar in un stato hemorrhagic. In nostre serie de plus que 125 casos, nulle fibrinolyse ha occurrite, sed illo remane un possibilitate. Derivationes de duration inusualmente prolongate o derivationes traumatic pote resultar in le depletion de certe factores coagulatori, con disturbationes de particularmente le prime phase del coagulation. Iste defecto es spontaneemente auto-limitatori. Es delineate methodos pro evitar iste difficultates e pro tractar los si illos occurre nonobstante.

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## A STUDY OF COMBINED MITRAL AND AORTIC STENOSIS \*

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## MATERIAL.

A STUDY was made of 141 patients treated by combined mitral and aortic commissurotomy during the interval from April, 1953, to May, 1958. There were 52 males and 89 females who had mitral and aortic stenosis, either alone, or in combination with adynamic, physiologically insignificant aortic and/or mitral regurgitation. Their ages ranged from 23 to 67.

## METHODS

In all cases, an analysis was made of the complete symptomatic pattern, including the electrocardiogram and chest roentgenogram. These observations, where possible, were compared with those obtained in a larger series of cases with pure mitral and aortic stenosis.

In addition, combined heart catheterization was performed in eight patients and left heart catheterization in an additional 23 by technics previously described.1,2

Cardiac output was calculated by the direct Fick method, while blood oxygen was determined by the method of Van Slyke and Neill.8 The respiratory gases were analyzed with the aid of a Pauling gas device. Pressure gradients were calculated by planimetric integration, while valve areas, pulmonary resistance and ventricular work were calculated by a modification of the formulae of Gorlin and Gorlin.4

## RELATIVE INCIDENCE OF COMBINED MITRAL AND AORTIC STENOSIS

Exact figures on the relative incidence of obstructive lesions of the cardiac valves in rheumatic heart disease have been difficult to obtain. The lack of good methods (until recently) for assessing mitral and aortic regurgitation is partly responsible for this.5 With the advent of cardiac surgery, exploration of the valves at surgery has been possible, so that a better classification of valve function can be made.

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At our clinic, 2,000 cases with mitral stenosis have been observed over a 10-year interval since 1948, as compared to 350 with aortic stenosis and 141 with combined mitral and aortic stenosis.

It should be pointed out that this is a selected series which is influenced by several factors. Surgery for mitral stenosis has been done for a longer period of time than that for aortic stenosis, with a lower mortality rate and generally better results. While closed aortic commissurotomy has been available since 1952, there has been a natural reluctance on the part of many physicians to refer their patients for this type of surgery until the recent advent of open technics.

TABLE 1
Symptomatic Pattern in Obstructive Rheumatic Valve Disease

Symptoms	Valvular Lesions		
	Mitral Stenosis Aortic Stenosis	Mitral Stenosis	Aortic Stenosia
Rheumatic fever Dyspnea Fatigue Edema Nocturnal dyspnea Angina Hemoptysis Emboli Syncope	52% 94% 87% 63% 36% 23% 32% 20%	62% 90% 93% 67% 33% .25% 18% 29%	27% 89% 88% 25% 21% 49% 0

## RHEUMATIC FEVER (TABLE 1)

A previous history of rheumatic fever was obtained in 52% of cases of combined mitral and aortic stenosis. This incidence is appreciably higher than in the group with isolated aortic stenosis (27%), and slightly lower than in patients with pure mitral stenosis (62%). The reason for these differences is not apparent.

# SYMPTOMATOLOGY (TABLE 1)

Dyspnea, the subjective sensation of the need for increased ventilation, and fatigue develop almost simultaneously in patients with combined mitral and aortic stenosis. They are early complaints which appear in 94% and 87% of the cases, respectively. The pattern was similar in isolated mitral and aortic stenosis. Any explanation of the mechanisms involved must be considered to be speculative, although the serious limitation of cardiac output in this disease is probably of prime importance. The maximal oxygen uptake is below normal, and, as breathing increases on exercise, it becomes less efficient. Finally, there may be impaired diffusion of oxygen across the alveolar membrane and a reduction in ventilatory performance secondary to pulmonary congestion.

When the latter is present, hemoptysis may develop. It was noted in 32% of this series, as contrasted to an incidence of 18% in pure mitral stenosis. None of our patients with isolated aortic stenosis mentioned this complaint. With severe degrees of dyspnea or with hemoptysis, cough was common. Generally, it was paroxysmal and productive of only minimal amounts of mucus; sometimes, it initiated the attacks of dyspnea.

Attacks of nocturnal dyspnea occurred with almost equal frequency in the group with combined obstructive disease and in those with isolated mitral stenosis (36% and 33%, respectively). One might postulate that this develops because of drop in the pulmonary vascular resistance during sleep, with a sudden surge of blood from the right ventricle. In patients with aortic stenosis, a different mechanism must be evoked. The increased resistance to ejection eventually causes elevation of the hydrostatic pressure in the pulmonary capillary bed, leading to edema in 21%. In all three categories, this symptom may appear in the presence of decreased pulmonary lymphatic drainage and increased pulmonary inflow secondary to altered systemic venous distensibility.<sup>8</sup>

Discharge of clot from the heart into the periphery almost never occurs in aortic stenosis, but this complication appeared in 20% of the combined cases, and in 29% of those with isolated mitral stenosis. It is more often seen in the presence of atrial fibrillation. The site of origin of the embolus frequently could not be located at surgery, despite thorough inspection of the heart chambers.

While true angina is rare in mitral stenosis, typical coronary pain is reported in almost half of the cases with aortic stenosis, and in 23% of those with combined mitral and aortic stenosis. It develops in response to the hypertrophy of the left ventricle, a decreased head of pressure at the coronary ostia, and interference with late systolic filling of the coronary tree because of the vigorous contraction of the left ventricle.

Syncope is twice as common in patients with isolated aortic stenosis (31%) as in those with combined lesions. There is no adequate explanation for this discrepancy.

As far as the manifestations of right heart failure are concerned, pure mitral stenosis and combined mitral and aortic stenosis reveal no sharp differences. Ankle edema was present in 67% of the former and in 63% of the latter, in contrast to only 25% of patients with isolated aortic stenosis. Hepatomegaly was common and ascites rare.

It seems reasonable to relate right heart failure to an elevated pulmonary vascular resistance, especially if mitral stenosis is present. Unfortunately the final pathways which lead to an elevation of the pulmonary vascular resistance have yet to be elucidated.

## CARDIAC AUSCULTATION

A rough midsystolic ejection murmur, loudest in the second right interspace, was present in all cases. The murmur was well transmitted to the

neck, suprasternal notch and the apex. It was not musical. Systolic thrills were common over the area of greatest intensity of the murmur. In 22% A2 was normal because the fibrotic and calcific process had not completely eliminated valvular mobility. In some, a faint or diminished aortic second sound was related to clockwise rotation of the heart, placing the aorta closer to the left sternal border.

Presystolic gallop sounds were common. In 68% an early diastolic murmur, usually quite faint, could be made out along the left sternal border.

In most patients, P2 was loud and not reduplicated. Paradoxic splitting was uncommon.

At the apex, the transmitted rough murmur of aortic stenosis was often altered in quality, becoming higher pitched. It usually was less intense in that area. Some of these changes may be related to preferential transmission of those components in the same frequency range as the natural frequency of the thorax. In 19% an independent pansystolic apical regurgitant murmur was present, blowing in character, and loudest in an area close to the anterior axillary line. It was hard to separate from the transmitted aortic murmur.

M<sub>1</sub> was not so sharp or snappy as in pure mitral stenosis, and the opening

snap was less easily identified.

The characteristic murmur of mitral stenosis was present in 97%. It was sometimes hard to make out because of noise produced by the transmitted basal murmurs, as well as the lack of the usually impressive ancillary auscultatory findings of mitral stenosis. As might be expected, the intensity and duration of this murmur correlated poorly with the severity of the mitral obstruction on left heart catheterization and surgical exploration of the valves.

## CHEST X-RAY

In 84% of cases the heart was moderately enlarged on roentgenologic examination (greater than 1 plus, based on a grading system of 0 to 4 plus). Left atrial dilatation was present in every patient but never assumed massive proportions, as it sometimes does in mitral regurgitation and rare forms of mitral stenosis.

The major arteries were studied. The pulmonary artery, or one of its major branches, was invariably increased in size, and a straightening of the left upper cardiac border was frequently found. In contrast, the ascending thoracic aorta was dilated in less than 20% of cases, even after careful examination of the patient in the left anterior oblique position.

It can be concluded that a typical configuration of the heart in combined mitral and aortic stenosis cannot be recognized (figure 1). Generally, the picture resembles that seen in mitral stenosis, rather than in isolated aortic stenosis. The appearance of the cardiac silhouette could not be related in predictable fashion to operative findings or hemodynamic data.



Chest roentgenograms in a patient with combined mitral and aortic stenosis. Note elongation of the left ventricle and prominence of pulmonary artery segment. Left atrium is moderately enlarged. FIG. 1.

## ELECTROCARDIOGRAMS

A standard 12-lead electrocardiogram provided evidence for right ventricular hypertrophy in 15%, for left ventricular hypertrophy in 18%, and for combined ventricular hypertrophy in 4%. Atrial fibrillation was present in 47%, while the remainder had a normal sinus rhythm. A completely normal electrocardiogram was present in 13%.

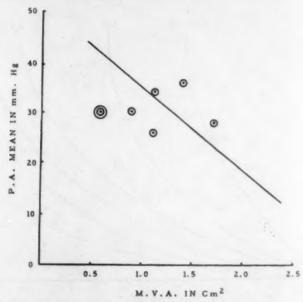


Fig. 2. Relation of mean pulmonary artery pressure and mitral valve area in combined mitral and aorfic stenosis.

#### CARDIAC CATHETERIZATION

The cardiac index was below normal in all, averaging 1.8 L./minute/m.²BS. This was considerably below the mean of 2.4 L./minute/m.²BS recorded in patients with pure aortic stenosis ° and the 2.2 L./minute/m.²BS reported in cases of pure mitral stenosis.<sup>30</sup>

The mean left atrial pressure was elevated in most, and averaged 21.6 mm. Hg, with a range of 8 to 35. Almost identical values have been reported in pure mitral stenosis. The "a" wave of the pressure pulse curve predominated in those patients with a normal sinus rhythm, and the "c" wave was often superimposed upon it. However, no finite analysis of the different components of the pulse curve was attempted. The mean left atrial pressure was lower in patients with normal sinus rhythm than in those with atrial fibrillation. In general, it was a function of the degree of the

mitral valve flow, and the high left ventricular diastolic pressure, as well as the inherent elasticity factors, which partially regulate the pressure-volume relationships in the chamber.

A pressure gradient across the mitral valve during ventricular filling was noted in every patient. It averaged 13.3 mm. Hg, with a range of 5 to 27 mm. Hg. In 17, it was greater than 10 mm. Hg. This range and mean were almost identical to those reported in pure mitral stenosis.<sup>10</sup>

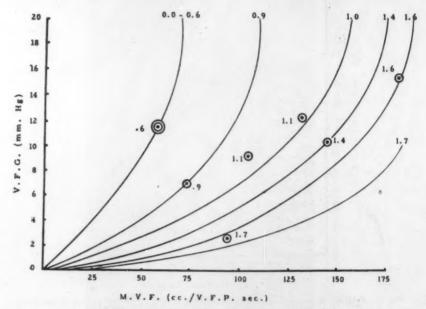


Fig. 3. Comparison of the left ventricular pressure filling gradient with mitral valve flow at different mitral valve areas in combined mitral and aortic stenosis.

The mitral valve flow was reduced in all, and ranged from 58 to 174 ml./ V.F.P. sec. It was below normal in all but two patients. The mitral valve areas ranged from 0.8 to 1.7 cm.², with an average area of 1.12 cm.² The calculated areas correlated poorly with the level of pulmonary artery pressure (figure 2). In pure mitral stenosis, the mitral valve areas averaged 1.2 cm.² in 35 cases.¹o

At constant valve areas, increase in flow was accompanied by an increase in gradient. For a given increase in flow, an increase in pressure gradient was most significant in smaller rather than larger valve areas (figure 3).

Mean pulmonary artery pressures ranged from 25 to 32 mm. Hg. Markedly elevated mean pressures (40 mm. Hg or higher) were not observed. Thirty-seven per cent of patients with mitral stenosis and 13%

of patients with aortic stenosis in a similar type of study exceeded these valves, ranging as high as 85 mm. Hg.

The pulmonary vascular resistance was normal in two patients and mildly elevated in the rest, with a range of 114 to 463 dynes sec. cm.<sup>-5</sup> Fourteen per cent of cases of pure aortic stenosis had higher values, while nearly 32% of cases of pure mitral stenosis fell into this elevated group. In one of the latter patients it measured 1680 dynes sec. cm.<sup>-5</sup>

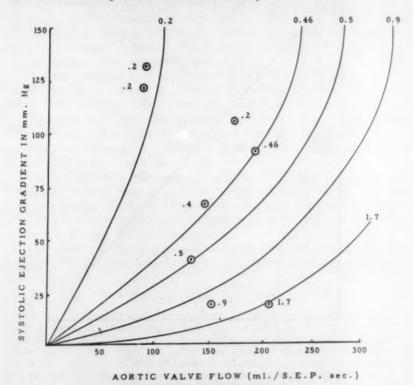


Fig. 4. Comparison of systolic ejection pressure gradient and aortic valve flow at different valve areas in combined mitral and aortic stenosis.

Total right ventricular work was not increased in any, and ranged from 0.43 to 0.99 Kg. m./min./m.², contrasting sharply with what was observed in mitral stenosis alone.

The aortic valve flow was reduced in all but one patient, ranging from 70 to 208 ml./S.E.P. sec. and averaging 110.9 ml. This is less than the mean of 164 ml./S.E.P. sec. reported in pure aortic stenosis.

The systolic ejection pressure in the left ventricle was elevated in all but eight patients, with a range of 110 to 255 mm. Hg. Similar findings were

observed in isolated aortic obstructive disease. Elevation of end diastolic pressures in the left ventricle was common to both groups.

A systolic ejection gradient was commonly observed across the aortic valve, ranging from 16 to 158 mm. Hg. It averaged 49.8 mm. Hg in the total group. Since the gradient is dependent not only upon the degree of obstruction but also upon the rate of flow, it is not surprising to find lower systolic ejection gradients in patients with combined disease than in the pure aortic obstructive group.

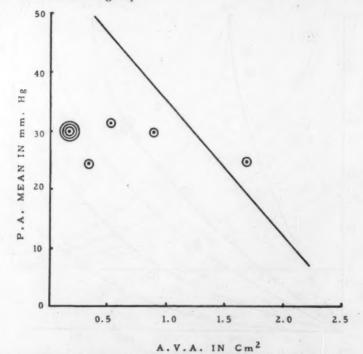


Fig. 5. Relation of mean pulmonary artery pressure and aortic valve area in combined mitral and aortic stenosis.

The aortic valve areas were critically reduced, ranging from 0.2 cm.<sup>2</sup> to 1.7 cm.<sup>2</sup>, with an average area of 0.57 cm.<sup>2</sup> These data were similar to the average area of 0.6 cm.<sup>2</sup> in the group of pure aortic stenosis. This is far below the estimated normal of 3 cm.<sup>2</sup> Again, as expected, for a given valve area the gradient varied as the rate of flow (figure 4). The valve area correlated poorly with the level of the pulmonary artery pressure (figure 5).

The total work of the left ventricle was increased in three patients. The average was 3.75 Kg. m./min./m.², which is just at the upper range of normal, and is lower than in patients with isolated aortic stenosis.

## SUMMARY

A review was made of the clinical and hemodynamic pattern in 141 surgically proved cases of combined mitral and aortic stenosis. When possible, comparisons were made with a larger series of 2,000 cases of pure mitral stenosis and 350 cases of pure aortic stenosis.

In combined mitral and aortic stenosis, as in isolated mitral or aortic stenosis, associated dyspnea and fatigue are present in nearly nine out of 10 cases. Like pure mitral stenosis, six to seven out of 10 have edema. Three out of 10 have hemoptysis, two out of 10, emboli, and nearly four out of 10, nocturnal dyspnea. The incidence of angina and syncope is half of that encountered in pure aortic stenosis.

A rough murmur of aortic stenosis was heard in all cases.  $A_2$  was normal in only two out of 10. The ancillary signs of mitral stenosis were often unimpressive, but the murmur was heard in almost everyone.

The chest roentgenogram resembles that seen in pure mitral stenosis. The heart size was significantly increased in more than eight out of 10.

The electrocardiogram revealed a pattern of right, left or combined hypertrophy in four out of 10.

Cardiac catheterization demonstrated similar valve areas in the combined and isolated obstructive valve lesions. Cardiac output was compromised to a greater degree in the combined group. In the latter disease, marked elevation of the calculated pulmonary resistance and mean pulmonary artery pressure was not encountered.

The results of the surgical treatment of combined mitral and aortic stenosis and the criteria for selection for surgery are outlined in a companion article.<sup>12</sup>

### SUMMARIO IN INTERLINGUA

Esseva effectuate un studio clinic e physiologic de 141 chirurgicamente confirmate casos de combinate stenosis mitral e aortic. Le resultatos esseva comparate con datos colligite ab 2.000 casos de pur stenosis mitral e ab 350 casos de pur stenosis aortic. In le gruppo combinate, un historia de febre rheumatic esseva incontrate in 52% del casos. Quasi 90% del patientes del gruppo combinate habeva dyspnea e fatiga, generalmente como gravamines initial. Dyspnea nocturne esseva notate in 36%, hemoptysis in 32%, embolisation in 20%. Edema esseva presente in 63%, angina o syncope in minus que 20%. Le conclusion es que le configuration del symptomas in combinate stenosis mitral e aortic representa un fusion de illos incontrate in isolate stenosis mitral e aortic.

In le auscultation cardiac, un aspere murmure de ejection mesosystolic esseva identificate in omne le casos. A2 esseva reducite o absente in 78% del casos. A1 apice, un murmure postmesodiastolic esseva audibile in omne le casos con le exception de 3%. Fibrillation atrial esseva presente in 47%.

Le examine roentgenologic revelava grados significative de allargamento cardiac in 84% del casos.

Le electrocardiogramma demonstrava hypertrophia dextero-ventricular in 15%, hypertrophia sinistro-ventricular in 18%, e hypertrophia ventricular combinate in 4%. Catheterismo cardiac combinate esseva interprendite in octo casos e catheterismo

solmente sinistro-cardiac in 23. Le indice cardiac esseva infra le norma in omne casos. Le valor medie del indice cardiac esseva 1,8 l/min/m². Le tension sinistro-atrial medie esseva elevate a 21,6 mm de Hg. Esseva constatate leve grados de elevation del tension pulmono-arterial e del resistentia pulmono-vascular. Le gradiente del pression de replenamento sinistro-ventricular esseva augmentate a 13,3 mm de Hg, durante le gradiente de ejection systolic trans le valvula aortic amontava a 49,8 mm de Hg. Le area del valvula mitral esseva reducite a 1,2 cm² e le area del valvula aortic a 0,57 cm².

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## DIAGNOSIS OF CHRONIC AORTO-ILIAC OCCLUSIVE ARTERIAL DISEASE\*

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THE syndrome of chronic aorto-iliac occlusive arterial disease begins when the occlusive process impairs the flow of blood enough to cause clinically recognizable symptoms and signs of arterial insufficiency. The occlusion usually results from a thrombus superimposed upon an area of localized atheroma formation. Occasionally, large atheromas only partially occlude the lumen but produce enough functional narrowing to cause symptomatic arterial insufficiency. The most common symptom of arterial insufficiency is intermittent claudication, which is characterized by distress induced by exercise, usually walking, and is relieved within minutes by stopping and standing, if not by just slowing the pace.

This syndrome was for years grouped under the general classification of "arteriosclerosis obliterans" of the lower extremities, with the designation of its predominant symptom as "high intermittent claudication," but without any special attempt to localize the site of the occlusion. The anatomic localization of the occlusion became important only when satisfactory

methods of direct surgical treatment were developed.

The availability of surgical treatment has intensified interest in more precise diagnosis and prognosis. An adequate clinical evaluation should include an acquaintance with the patient's problem, and the application to it of what is known of the natural history of the disease, a complete examination of the peripheral vascular system of the patient, and a careful consideration of indications for special technics in diagnosis, as well as a consideration of the patient's general condition.

#### EVALUATION OF PATIENT'S PROBLEM

The syndrome of chronic aorto-iliac occlusive arterial disease can be recognized readily by a physician familiar with the characteristic symptoms of high intermittent claudication. As in most other peripheral vascular diseases, elaborate and expensive equipment or highly specialized diagnostic technics are not essential to the diagnosis or to the anatomic localization in patients with complete organic occlusion, and in few, if any, with partial atheromatous occlusion.

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Since in the majority of cases, when the patient first consults the physician, intermittent claudication is the only symptom or sign of arterial insufficiency below the occluded site, proper identification and evaluation of this symptom are paramount in the diagnosis and evaluation for treatment. I have often obtained revealing information by asking the patient a direct question, such as, "How much does this symptom interfere with what you have to do as compared with what you would like to do?" After thinking for a minute, most patients will reply that it does not interfere much with what they have to do. This reply does not necessarily mean that the limitation of walking is unimportant to every patient, as shown by one patient's sincere answer to the effect that he would rather be dead than not be able to keep up with his partners in their twice-a-week golf games. He had a successful by-pass operation and two years later was still enjoying his golf. If the answer is that the symptom does interfere seriously with what he has to do, this often will be in relationship to a type of work that requires some sustained physical activity, and it usually will indicate a degree of disability significant enough to justify serious consideration of direct surgical treatment

It is sometimes difficult to obtain a clear indication from the history alone as to how much the difficulty in walking interferes with a patient's livelihood and happiness. The success of the "two or three cars in every garage" sales-promotion philosophy has now made it unnecessary to walk very far, and, in fact, almost impossible for anyone living in even a small city to walk more than one block without stopping for a traffic light, or for an automobile or two to pass through the crosswalk.

If there is uncertainty from the history as to how limiting the intermittent claudication is, a standard walking test should be done to evaluate the symptom properly.

As an example of how important an objective evaluation may be in some cases, I recently examined a 67-year-old man who was very anxious to have a by-pass operation for relief of what he said was disabling distress in his lower extremities when he walked as far as one or two blocks. In fact, a physician had already urged him to have an operation for relief of this symptom. Standard walking tests, carried out on a walking machine and by supervised walking at a measured pace on a sidewalk, revealed that he actually could walk continuously at least 18 minutes without enough distress to make him slow his pace significantly or stop walking. Further inquiry into the history revealed emotional reasons for his strong desire to have an operation for his occlusive arterial disease. He thought that his poor circulation would prevent him from keeping up with his young, golf-playing, prospective bride. Another symptom of aorto-iliac occlusive arterial disease about which this patient also may have been concerned was inability to have and maintain an erection of the penis. It is not certain how often this is due to an interference of blood supply to the penis caused by the aorto-iliac

obstruction, and how often it is just the natural consequences of "growing old along with me." I do not know of any well controlled study that has determined this point. Until we have this information, we should not consider the possibility of restoring this function as among the valid reasons for advising surgical treatment.

In another case a walking test showed that a serious disability in walking was due to muscular weakness from early amyotrophic lateral sclerosis. A coincidental and symptomatically unimportant segmental occlusive arterial disease, for which an operation had been advised, was also present. Table 1 shows a number of conditions the symptoms of which have been mistaken for those of occlusive arterial disease.

#### TABLE 1

Conditions in Which Predominant Symptoms May Simulate Those of Atherosclerotic Occlusive Arterial Disease

- 1. Abnormalities affecting muscle function primarily:
  Muscular dystrophy
  Amyotrophic lateral sclerosis
  Progressive muscular atrophy
  Myasthenia gravis
  Hyperthyroidism
  Marked anemia
- Skeletal or neurologic conditions:
   Protruded lumbar disk, spinal cord tumor Metastatic malignant disease of lumbar spine Degenerative arthritis of hip joints Shortened Achilles tendons
- Other types of vascular diseases:
   Congenital coarctation of aorta
   Ergot sensitivity with spastic occlusion of iliac arteries
   Occlusion of inferior vena cava
   Orthostatic hypotension

## EVALUATION OF PERIPHERAL VASCULAR SYSTEM

In the physical examination, careful palpation will disclose that pulsations are diminished or absent in the lower part of the abdominal aorta and below the bifurcation of the aorta. Examination may reveal varying degrees of coldness of the feet and legs, and some pallor of the feet on elevation of the lower extremities. These changes are usually not marked unless the abdominal aorta and its collaterals are occluded extensively. A systolic murmur may be heard over the lower part of the abdomen and over the lumbar region.

Laboratory findings and plain roentgenograms are of little aid in the diagnosis of occlusion of the abdominal aorta, although a roentgenogram of the region of the abdominal aorta may reveal varying degrees of calcification of that vessel. An aortogram usually visualizes the site and degree of the obstruction, and may reveal additional sites of obstruction in the iliac and upper portions of the femoral arteries if such sites are present. It

also shows the relationship of the site of obstruction to the renal and mesenteric arteries, and gives some information of value concerning collateral circulation. The aortogram does not always reveal correctly all details of the true situation.

In the evaluation for possible surgical treatment it is important to determine whether occlusive arterial disease exists above or below the segmentally occluded aorto-iliac site. In my experience it is possible in many cases to determine whether there is distal occlusion on the basis of the history and physical findings alone.

One should suspect another site of occlusion, usually in the femoral artery, if the patient first had intermittent claudication localized to the calf muscles, and later had high intermittent claudication, or if, subsequent to the initial high localization, he developed claudication in the calf which now stops him before the initial symptom of high claudication can occur. A history of subsequent acute arterial occlusion or the sudden development of uremia or hypertension usually means that another occlusion has occurred above or below the original site in the aorto-iliac region.

Evidence on the original physical examination of more than a mild degree of ischemia in the feet, or especially in one foot, as indicated by a high degree of coldness and pallor on elevation, or a marked delay in venous filling when the legs are dependent, suggests other sites of occlusion. Ischemic neuropathy, ischemic ulcers or gangrene is uncommon in uncomplicated aorto-iliac occlusion. In support of these statements are the findings of Massarelli and Estes, presented at the meeting of the American College of Physicians in 1957, that in their group of 105 patients with atherosclerotic aorto-iliac occlusive disease, distal ischemia (of more than mild degree as determined by the elevation-dependency test), ischemic neuropathy, ulcer and gangrene were infrequent. Objective evidence of more than a mild degree of ischemia is almost never found in those patients who have been proved by arteriographic means or by direct examination to have no occlusion distal to that in the aorto-iliac region.

## STATEMENTS VERSUS FACTS

Someone has said that we make the same mistakes a thousand times and call it clinical experience. Five years ago, in a discussion of the diagnosis of aorto-iliac occlusive arterial disease, my statements concerning the natural history of the disease had to be based largely on clinical experience. When these statements are viewed in the light of more factual information supplied by Massarelli and Estes, and in the light of a study just completed by my colleagues and me, the validity of this axiom in regard to the clinical evaluation of aorto-iliac occlusive arterial disease is borne out.

I would like to repeat some of these statements, \$, 4 and then tell you what we now think are the facts.

Statement 1: "Frequently, periaortitis is present and causes adhesion

to the vena cava and other structures in the region." The fact is, it is rare. We at first had been operating only on patients with the most severe symptoms who had, in some cases, constant pain and soreness in the abdomen in addition to intermittent claudication.

Statement 2: "Later in the course of the disease, the distance that can be walked without distress is lessened and in many instances may be reduced to less than one block." The truth is, in about half of the patients there is no lessening of the distance they can walk, and many of the patients on a conservative program of treatment or on no treatment find in later years that they can walk further.

Statement 3: "The disease is usually progressive over a period of five to 10 years." If the disease has been present for two years or longer, and has shown no signs of progression, there is seldom any progression of symptoms, nor is there development of serious complications of ischemia in many

of those patients who do not have diabetes.

Statement 4: "Not infrequently the thrombus may extend upward to involve the renal and superior mesenteric arteries." Although the problem of proximal occlusion with involvement of the renal or mesenteric arteries may arise, it occurs so rarely that it does not routinely require detailed analysis or aortographic investigation. Massarelli and Estes <sup>1</sup> found no patient in their series who had occlusion of the renal artery causing uremia. In the follow-up study just completed by my colleagues and myself we found only two instances of the subsequent development of renal-artery occlusion that had caused hypertension or uremia.

Statement 5: "Inability to maintain an erection of the penis commonly ensues." This distressing situation, due only to ischemia, is probably uncommon. I have already discussed the diagnostic implications of this

symptom.

Statement 6: "Some patients maintain themselves for a number of years without evidence of gangrene or other serious disability." If diabetes is not present, about 90% of these patients maintain themselves for a number of years without evidence of gangrene or other serious difficulty.

#### ANGIOGRAPHY

In the short time remaining, I would like to discuss the indications for angiographic examination, which necessarily will include statements bearing on operability, and then to summarize my ideas as an internist as to the

general indications for surgical treatment.

The main indication for angiographic examination is the potential candidacy for surgical treatment. If the patient obviously is not suitable for operation, the risk, inconvenience and expense of the procedure are not justified. I have already indicated that, from a clinical evaluation alone, without angiographic information, it is often possible to determine many important points bearing on the suitability for surgical treatment of the

aorto-iliac region. Although aortography is a safe procedure when performed properly, it should be done only when it is clearly indicated. I cannot improve on the questions which my colleague, Dr. Estes, has suggested that a physician ask himself before advising angiographic examination: 1. Will the test provide essential information that is not already available? 2. Can this information be obtained by a simpler and less expensive method? 3. Will this information permit more effective treatment of the patient? 4. Inasmuch as angiographic examination is usually a prelude to surgical treatment, are the patient's age and general health such that surgical treatment or angiographic examination is justifiable? 5. Are the patient's symptoms of sufficient severity to warrant surgical treatment? 6. Are there any contraindications to angiographic examination (bleeding disorder, current anticoagulant therapy, sensitivity to radiopaque substances)? 7. Has the patient elected to proceed with this test, understanding that it is only a diagnostic measure to aid in determining operability?

If the answer to the questions is "yes," then the angiographic procedure

may be advised with assurance that it is justified.

## INDICATIONS FOR SURGICAL TREATMENT

The indications for surgical treatment should be based largely on an evaluation of the degree of functional impairment of blood flow, as well as on an estimation of prognosis, if surgical treatment is not done, for the individual patient being examined. The tendency of some physicians to consider mainly the local anatomic situation is not in the best interest of the patient.

One should remember that surgical treatment is elective and palliative. Consequently, the indications for it should largely concern an evaluation of the specific symptoms of ischemia, the general condition of the patient, and the presence or absence of significant symptomatic atherosclerotic disease elsewhere in the body. The surgeon can make good use of the broad clinical experience of the general physician and internist in helping to decide which patients should be advised to submit to direct arterial surgical treatment for chronic aorto-iliac occlusive arterial disease. I believe that a careful clinical evaluation of every patient along the lines I have outlined will clarify the indications for surgical treatment and thereby keep this valuable form of treatment of occlusive arterial disease from becoming another example of the "triumph of technic over reason."

#### SUMMARIO IN INTERLINGUA

Occlusion chronic del aorta abdominal e del arterias iliac es characterisate symptomatologicamente per le disveloppamento gradual de fatiga e dolores dorsal, coxal, e femoral, occurrente solmente in exercitio e alleviabile per le arresto del movimento, Frigor e pallor del extremitates inferior e le incapacitate de experientiar o de mantener un erection del penis es aspectos que occurre sed que es inusual.

Un meticulose palpation revela que le pulsationes es reducite o absente in le parte inferior del aorta abdominal e infra le bifurcation del aorta. Il es possibile que le examine physic revela frigor del pedes e del gambas e un certe grado de pallor del pedes quando le extremitates inferior es elevate. Usualmente iste alterationes non es marcate, excepte quando le aorta abdominal es occludite extensemente o quando le arterias infra le bifurcation del aorta es occludite. Un murmure systolic es a vices audibile supra le parte inferior del abdomine e, in certe casos, in le dorso supra le region lumbar.

Studios laboratorial e roentgenographia conventional es de pauc valor in le diagnose de occlusion del aorta abdominal. Un aortogramma reveia usualmente le sito e le grado de obstruction in le aorta e possibilemente sitos additional de obstruc-

tion in le portiones iliac e superior del arterias femoral, si tales es presente.

Le duo desideratos diagnostic que es del plus grande importantia con referentia al question del therapia es (1) determinar per medio de un meticulose studio del historia del caso a qual grado le symptoma de claudication intermittente disturba de facto le utilitate e le felicitate del patiente individual e (2) determinar, in tanto que possibile, si le un o le altere del grande arterias distal al bifurcation del aorta es occludite.

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# SURGICAL ASPECTS OF OCCLUSIVE DISEASE OF THE AORTA AND ILIAC ARTERIES\*

By Alfred W. Humphries, M.D., Victor G. DeWolfe, M.D., F.A.C.P., FAY A. LeFevre, M.D., F.A.C.P., and R. C. Britton, M.D., Cleveland, Ohio

It is our purpose in this brief paper to present the current philosophy of the medicosurgical vascular team of the Cleveland Clinic regarding angio-

plastic procedures on the major peripheral vessels.

Experience with 750 arterial grafts has led to certain criteria which we follow in selecting candidates for arterial surgery. Although these criteria are subject to modification at any time, they establish our philosophy concerning arterial grafts at the present time. Thrombo-endarterectomy is occasionally done, particularly for carotid and renal stenosis, but most patients operated upon for arterial disease at the Cleveland Clinic have received either a homograft or a Dacron prosthesis.

## WHO CAN BE OPERATED UPON?

Before deciding whether a patient should be offered arterial reconstruction, one must first determine that surgery is technically possible. Successful restoration of blood flow depends upon a new blood *supply* from a proximal site, and also upon the *distribution* of this new supply to the distal vessels.

Successfully replacing or by-passing an occluded vessel results in a new blood supply to the main artery below the obstruction. This will not improve circulation, however, if the patient's own terminal distributional system is not patent. It must be realized that the ultimate purpose of arterial surgery is to increase the supply of blood to the individual cell, rather than merely to circumvent successfully an arteriosclerotic occlusion in a main artery.

The difference between the operable and the inoperable patient may therefore be clarified by defining the difference between a segmental and a nonsegmental occlusion (figures 1 and 2). In the segmental type of occlusion the continuing vessels are open, and the blood supplied by the graft has a means of egress. In the nonsegmental form there is no distal point to which the graft may be attached, and so surgery is not feasible. The

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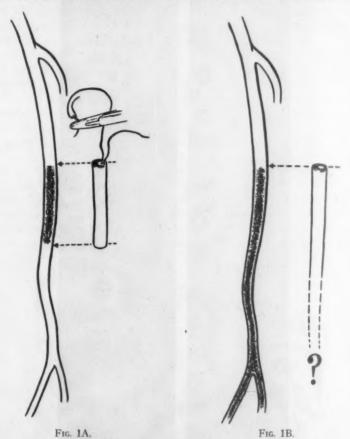
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length of the occlusion is not particularly important, but the presence of adequate outflow is critical.

As might be surmised, the more proximal the occlusion, the better the chances for an adequate outflow, since more channels of egress are available. Therefore, although inadequate outflow is encountered in an appreciable number of femoral occlusions, it is rare to find an aorto-iliac occlusion that



is not technically feasible. If the feet are viable in the presence of a high occlusion, either the superficial femoral or the deep femoral artery must be open to supply blood to the lower extremity. The size of these vessels is such that they almost invariably represent an adequate outflow.

The most difficult decisions lie in the intermediate zone between obvious operability and obvious inoperability. In these instances, some patent vessels may be seen on the arteriogram below the occlusion, but the blood-

carrying capacity of the vessels may be questionable. In the presence of severe arterial insufficiency, with rest pain, ulcer or gangrene, we usually elect to attempt a graft when the outflow is in doubt. This is based upon the thesis of having little to lose and a great deal to gain, since the graft is successful in a certain number of apparently impossible cases. If the outflow



Fig. 2A.

Fig. 2B.

is truly insufficient, the graft cannot and will not function. These "desperation" attempts account for the large number of "primary" failures in our series.

## WHO SHOULD BE GRAFTED?

It may be said that essentially all aneurysms should be replaced by a graft. In the case of occlusive disease, however, such a blanket statement cannot properly be made. The symptomatology of occlusive disease varies, depending upon the degree of anatomic vascular involvement. Occlusions circumvented by good collaterals with a comparatively mild interference to blood flow result in only intermittent claudication in the muscle group corresponding to the level of arterial occlusion (figure 3). Intermittent claudication is the mildest of the symptoms of arterial insufficiency. It is important to differentiate between progressive and nonprogressive intermittent claudication on the basis of history. Not all patients with claudication go on to increasing arterial involvement and increasing symptoms, and some patients with claudication maintain the same walking distance for years, or may even spontaneously improve. However, historical evidence of progressive claudication with decreasing walking distance, and therefore decreasing blood supply, may well presage more serious problems to come.

Further involvement beyond the stage of simple claudication occurs if the arteriosclerotic occlusive process extends, or if a thrombosis-in-situ is super-imposed upon a sclerotic stenosis. In this event the symptom of rest pain

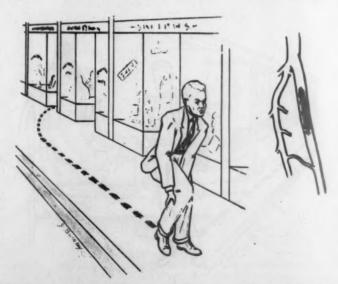


Fig. 3A. An occlusion of the superficial femoral artery generally causes claudication in the calf,



Fig. 3B. An occlusion of the iliac artery generally causes claudication in the hip and thigh.

or the development of an ulcer or even gangrene may supervene (figure 4). Under these circumstances, arterial flow is very seriously diminished and the need for restoration of flow is acute. Unfortunately, in many instances the outflow tract may no longer be open and a graft cannot be done.



Fig. 3C. An occlusion of the aorta or its bifurcation generally causes claudication in both hips.

To summarize, we feel that the group with rest pain, ulcer and gangrene should be operated upon immediately, the progressive claudicator should be operated upon within the near future, and the nonprogressive claudicators may or may not be grafted, depending upon other associated conditions, which are discussed below.



Fig. 4A. (above) Two occlusions at different levels will frequently interfere with blood supply to a sufficient degree to cause rest pain.

Fig. 4B. (below) Significant interference with the major collateral source in conjunction with a total occlusion of the main artery is frequently sufficient to cause gangrene.

## WHO SHOULD NOT BE GRAFTED?

Patients not suitable for direct arterial surgery may be divided into two large subgroups: those with associated prohibiting disease, and those with arterial involvement too minimal to require correction.

The first subgroup includes such associated disease as congestive heart failure, malignancy, incapacitation due to previous stroke, etc. Those with angina must be carefully evaluated and a decision made between the benefits to be derived from a satisfactory graft and the possible aggravation of cardiac insufficiency from the stress of the operation. Unless definitely indicated, the patient with angina pectoris should probably not be grafted, and the patient with angina decubitus should never be done. Past history of a coronary occlusion has not seemed to be a significant factor in our series

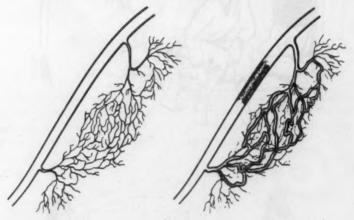


Fig. 5.

as long as the occlusion is old and has not resulted in serious angina. Severe renal involvement with arteriosclerotic nephrosclerosis or diffuse involvement of main-stem renal arteries usually contraindicates surgery unless there is imminent danger of amputation. Finally, patients with severe emphysema have had a high incidence of postoperative cardiopulmonary complications.

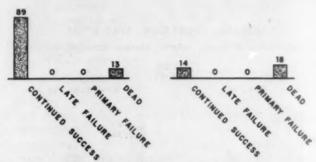
The second subgroup includes those patients whose difficulties are too mild to warrant correction. In a series of over 100 untreated patients with occlusive arteriosclerotic disease followed for five years, it was found that roughly 25% had spontaneous improvement, 50% remained the same, and approximately 25% became worse. It has become our custom to observe the patient with nonprogressive claudication, to encourage walking in the hope of stimulating further collateral development, and to do nothing definitive until such time as progression occurs.

# OVERALL OPERATION STATISTICS (Exclusive of renal, carotid, thoracoabdominal, etc.)

Aortic Aneurysm

ELECTIVE

HON-ELECTIVE



 $\begin{tabular}{lll} Fig. 6A. & Non-elective an eurysms are those where the an eurysm is symptomatic or frankly ruptured. \end{tabular}$ 

On the same grounds, we generally do not operate on the patient with a recent arterial occlusion who is improving. A sudden occlusion may go on directly to an ischemic limb. However, if the occlusion is not of suf-

# OVERALL OPERATION STATISTICS

(Exclusive of renal, carotid, thoracoabdominal, etc.)

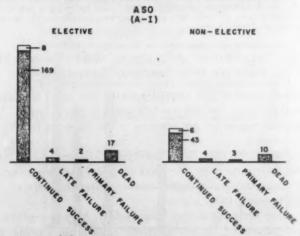


Fig. 6B. Those grafts included in the continued success column but without stippling represent grafts which have been successfully done again following a late failure of the initial graft. Elective cases are those who only claudicate; non-elective represent those with rest pain, ulcer or gangrene.

ficient extent to produce death of the limb, and collaterals are adequate, only claudication may result. As time goes on the collateral bed may increase (figure 5), with concurrent improvement in claudication, and arterial reconstruction may not become necessary. This subgroup also includes the patient with less serious disease in one limb than in the other which has an inoperable occlusion.

# 

Fig. 6C. Those grafts included in the continued success column but without stippling represent grafts which have been successfully done again following a late failure of the initial graft. Elective cases are those who only claudicate; non-elective represent those with rest pain, ulcer or gangrene.

# FOLLOWING THESE RULES OF SELECTION, WHAT RESULTS MAY BE EXPECTED FROM SURGICAL TREATMENT?

In a current series of 750 arterial grafts in the aorto-iliac and femoral areas followed for up to five and one-half years, it may be stated that results in the aorto-iliac region are satisfactory, while those in the femoral area require improvement.

Of the group with nonleaking aneurysms (figure 6A), 13 have died either during their surgery or later, and no grafts have since occluded. In the case of aneurysms, either symptomatic or frankly ruptured, the death rate is proportionately much higher.

In aorto-iliac occlusive disease (figure 6B), very few primary or late failures have occurred. In the "elective" (claudication only) group, for example, 169 original grafts, and eight done again after a late failure, are compared with two initial failures and 12 late shutdowns. Surprisingly,

TABLE 1 Graft Follow-up

371 01 700	
Arteriosclerosis Obliterans	
Aorto-iliac	
Elective Non-elective	177—12—93% 49—10—81%
Femoro-popliteal	
Elective Non-elective	$100 - 42 - 68\% \\ 77 - 35 - 66\%$
Aortic Aneurysm	
Elective Non-elective	89— 0—100% 14— 0—100%

the failure rate is only slightly higher in the "nonelective" group with rest pain, ulcer or gangrene.

In femoro-popliteal occlusive disease (figure 6C), however, the late shut-down rate rises sharply. Also, the incidence of primary failure is much higher, due to our willingness to attempt an "impossible" graft in the hope of saving an extremity. Again, there is little difference in success whether the patient only claudicates or has more serious involvement.

The above figures represent our over-all operative experience. The statistics of certain aspects of the results are perhaps more significant.

Table 1 indicates the continuing success rate on those grafts which were initially successful. Here the deaths and primary failures have been excluded, since these grafts could not be followed. Over periods ranging up

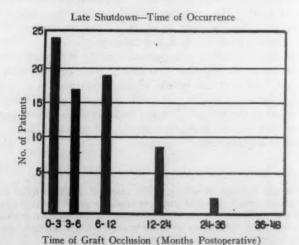


Fig. 7.

to five and one-half years, all of the grafts for aneurysm have remained open, roughly 90% of the elective aorto-iliac grafts for occlusive disease still function, 80% of the non-elective aorto-iliac grafts are patent, and almost 70% of the femoro-popliteal grafts remain successful.

Of interest (figure 7) is the observation that most of the failures have occurred within the first year following the placement of the graft. Advancement of the patient's own disease below the lower limits of the graft has been the most common cause of late failure.

Table 2
Functional Results in Late Failures Not Regrafted
68 of 574 = 12%

Better	Same	Worse
19	 37	(2% of total
		grafts)

Of the late failures (table 2) who for one reason or another have not been regrafted, 12 (2%) of the total were worse than before their graft.

### SYMPATHECTOMY

We have discussed to this point the treatment of occlusive arterial disease by a direct approach to the occluded artery itself. Sympathectomy also lies within the surgical armamentarium, and opinions regarding its usefulness vary. We never employ sympathectomy in the treatment of the patient whose only symptom is claudication. We almost routinely employ sympathectomy in the patient with rest pain or ulceration who is not a candidate for an arterial graft. We occasionally will combine sympathectomy with an arterial graft in those patients in whom we feel the outflow is probably sufficient to permit a graft but is not of the best.

In conclusion, although it is apparent from the foregoing that there is definite indication for the surgical treatment of some patients with occlusive arterial disease, and that the results of such treatment are in the main essentially satisfactory, there is still much room for improvement. Probably most needed at the present time are better criteria concerning the outflow tract, so that we can lessen the number of primary failures, each of which represents an unnecessary operation.

#### SUMMARIO IN INTERLINGUA

Le experientias colligite in plus que 750 casos de graffo arterial hia resultate in le formulation de certe criterios le quales es applicate per le personal angio-medical e angio-chirurgic al Clinica Cleveland in effectuar per consultation mutual le selection de candidatos pro operationes arterio-chirurgic. Certe aspectos del problema es discutite in le presente articulo. Illos es:

Qui deberea esser operate? Le objectivo del restauration chirurgic del fluxo arterial de sanguine, tanto per medio de graffos como etiam per medio de thrombo-

endarterectomia, es augmentar le provision de sanguine al ultime cellulas del histos. Ergo, a fin que un subjecto pote esser considerate como candidato pro le application de un graffo, il debe esser certe que le occlusion in su caso es de longor limitate e que in le areas distal al termination del occlusion il existe un patente vasculatura arterial. Si nulle distal systema distributional es presente con le qual le graffo pote esser ponite in anastomose, le patiente non es un candidato qualificate pro reconstruction arterial.

Qui deberea esser tractate per graffation? Claudication intermittente es le plus leve del symptomas de insufficientia arterial. Le reduction additional del fluxo de sanguine resulta in dolores in stato de reposo, e le perdita subtotal del fluxo de sanguine resulta in ulceres e gangrena. In summa, nos opina que le gruppo de patientes con dolores in reposo, con ulceres, e con gangrena debe esser operate immediatemente si illes es candidatos pro le uso de graffos. Subjectos con claudication progressive debe esser operate in un futuro non troppo distante. E finalmente, in le caso de patientes con claudication nonprogressive sed static, le question del application de un graffo arterial pote esser resolvite in le un o le altere senso, in dependentia del requirimentos social o economic inherente in le occupation del patiente.

Qui non deberea esser tractate per graffation? Patientes con associate morbos invalidante—congestive disfallimento cardiac, crescentias maligne, incapacitation per previe episodios syncopic, etc.—debe esser considerate (per definition) como non-candidatos pro le introduction de graffos. Patientes con angina de pectore, con rar exceptiones, non debe esser subjicite a graffation. Patientes con angina

decubital es non-candidatos, sin ulle exception.

Si iste criterios de selection es observate, qual resultatos pote esser expectate ab graffos arterial? In general, on pote dicer que approximativemente 90% del graffos aorto-iliac, selectivemente effectuate, va remaner successos durante periodos de usque a septe annos; que approximativemente 80% del graffos aorto-iliac, effectuate como operationes de urgentia pro ischemia sever, va remaner successos durante tal periodos de tempore; e que approximativemente 70% del graffos femoro-popliteal, effectuate selectivemente o nonselectivemente, promitte remaner successos in le mesme senso.

## PHYSIOLOGIC AND BIOCHEMICAL ASPECTS OF THE DISORDERED CORONARY **CIRCULATION\***

By RICHARD GORLIN, M.D., NORMAN BRACHFELD, M.D., JOSEPH V. MESSER, M.D., and JOHN D. TURNER, M.D., Boston, Massachusetts

DESPITE extensive anatomicopathologic studies, the characteristics of the coronary circulation responsible for ischemic heart disease have not been quantitatively defined. Recent advances in the measurement of coronary blood flow, combined with the technic of coronary sinus catheterization, 18, b, c have resulted in a physiologic approach to the dynamics of coronary flow in man. It is the purpose of this report to present the hemodynamic and biochemical characteristics of the coronary circulation in patients with angina pectoris. Our findings are based on a correlative clinical, electrocardiographic and cardiac catheterization study of 50 patients.

Coronary sinus catheterization was performed with measurement of coronary blood flow by the nitrous oxide technic in all individuals at rest.1b A second flow was determined following the sublingual administration of nitroglycerin in 37 individuals, and during exercise in 15. Cardiac output 2 and peripheral and pulmonary pressures were also measured. Calculations were made of myocardial oxygen consumption and its derivatives,8 coronary vascular resistance and left ventricular work.2 Of the group of 50 patients, 10 were judged to have normal or nearly normal hearts, 23 had angina pectoris, and the remainder had varying states which imposed an increased work load on the left or right ventricle. Electrocardiograms were recorded following exercise in all patients with clinical chest pain, both at the time of catheterization and as part of a standard exercise two-step test.

The heart is basically an aerobic organism. This has been well substantiated by the low content of anaerobic enzymes, the high concentration of cytochromes, 4a, b and the fact that the heart cannot perform a normal work load in the absence of oxygen. Thus, while the heart may "live" in the noncontractile state in the absence of oxygen for periods of up to an hour or more, such an environment will not permit contractile activity sufficient

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From the Medical Clinics, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

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to maintain normal cardiac output and blood pressure. The continuing need for oxygen by the heart is met by coronary blood flow and by rather complete oxygen extraction from each milliliter of blood. The coronary circulation is totally different from any other circulation in the body in that 75% of the oxygen presented to the myocardium is removed from the blood 6 (figure 1). As a result, changes in the need for oxygen become almost completely dependent upon changes in coronary flow. Further increase in extraction of oxygen occurs only as a final defense, when flow alone is no longer capable of meeting demand.

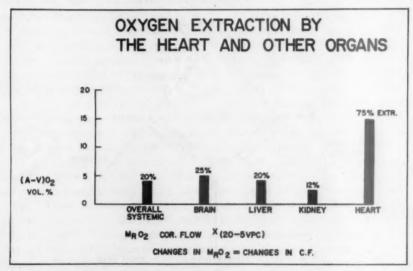


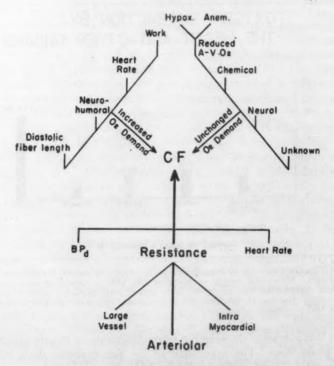
Fig. 1. This illustrates the striking difference in oxygen extraction between the heart and other organs. Myocardial oxygen consumption (M RO<sub>2</sub>) is dependent upon coronary blood flow and oxygen extraction (normally, 12 to 15 vol.% are extracted between coronary artery and vein). Because of the wide and near-maximal extraction at rest, changes in oxygen need lead to changes in coronary flow.

Figure 2 is a schema showing the interrelationship of factors governing coronary blood flow. The upper half of the figure shows those factors which demand a change in flow. To the left are seen those factors which do so by increasing the oxygen demand on the heart. Varying work of the heart is the most common cause of change in the need for oxygen supply. Studies by Evans and Matsuoka <sup>6</sup> and Sarnoff and co-workers <sup>7</sup> in dogs, and our own observations in man, <sup>8</sup> would show that, under acute conditions, alterations in blood pressure are much more costly in terms of oxygen and substrate supply than are alterations in cardiac output. On the other hand, studies carried out in man subjected to a chronic work load, as in clinical disease, indicate no such dramatic difference between the high flow work

loads and the high pressure work loads in terms of the oxygen cost to the heart.<sup>9</sup> Aortic insufficiency resulted in as great a need for oxygen by the myocardium as did aortic stenosis.<sup>8</sup> Cardiac rate, when it increases, also increases the need for oxygen in direct proportion to systolic contraction time.<sup>8</sup> Epinephrine <sup>10</sup> and thyroid hormones <sup>11</sup> and changes in diastolic fiber length <sup>12</sup> likewise increase myocardial oxygen cost.

## REGULATION OF CORONARY BLOOD FLOW

## DEMAND FOR CHANGE



## MECHANISM OF CHANGE

Fig. 2. Discussion in text.

On the right are seen those factors affecting the normally low flow/extraction ratio. The factor which most commonly affects this ratio is a reduction in oxygen content of coronary arterial blood, as with anemia or anoxemia. The normal oxygen needs must be met by an increased coronary flow. Certain chemical, neural and unknown mechanisms may likewise alter the flow/extraction ratio.<sup>18</sup>

How, then, are these flow demands met? The major hydraulic factor is the aortic perfusion pressure, and because the coronaries are perfused primarily in diastole, the mean diastolic blood pressure is of greatest significance. Similarly, the duration of diastole is important. Increased cardiac rate has a deleterious action on coronary hemodynamics, not only by increasing oxygen consumption, but also by decreasing diastolic inflow time.3 The second most important factor in the regulation of coronary flow is vascular resistance. Resistance to flow may be the result of myocardial compression, direct obstruction of the large coronary arteries, or constriction of the arterioles. An increased demand for coronary blood flow which is not accompanied by an increase in aortic perfusion pressure is usually met by arteriolar dilatation and decreased coronary vascular resistance. Similarly, when mechanisms of supply are compromised, as, for example, with the low diastolic pressure of aortic insufficiency, with tachycardia, or when the intramvocardial resistance in systole is infinite, as in aortic stenosis, there is a compensating coronary vasodilatation. The increased need for oxygen and the resultant increased coronary flow imposed by these pathologic states are met by even further arteriolar dilatation. In similar fashion, when coronary artery disease is diffuse, with narrowing or obstruction of many large blood vessels, the coronary circulation is kept at a functioning level compatible with normal muscle action through the mechanism of arteriolar vasodilatation. 148, b Thus, as coronary sclerosis progresses, collateral anastomoses open up and arterioles distal to the obstructed vessel dilate. These mechanisms become most important because of the inability of the heart to bud new blood vessels in relation to demand, a reactive response found in many other organ systems. Indeed, Wearn has shown that, as the heart hypertrophies, the number of capillaries per muscle fiber decreases. 15 The natural corollary of this fact is that, when vascular disease becomes severe as well as diffuse, the available coronary arteriolar reserve for dilatation under stress is now compromised and inadequate. 16

It cannot be emphasized too strongly that, due to collateral dilatation, coronary blood flow is perfectly normal or even slightly increased at rest in patients with angina pectoris. Therefore, one can learn little about the state of the coronary circulation without a measure of its reserve capacity.

How may these physiologic deviations from the normal be investigated? We have studied our patients in two ways. The first was by the administration of a vasodilator, nitroglycerin, to compare the ability of the coronary circulation to dilate in the normal and the abnormal patient. These observations will be reported in detail elsewhere. Figure 3 is a summary of our findings. Normally, the coronary blood flow doubles following the administration of nitroglycerin, with a 50% decrease of coronary vascular resistance. This is accomplished without change in the coronary arteriovenous extraction of oxygen, and therefore a rise in myocardial oxygen consumption per minute in relation to work done. The increased velocity

of blood flow has also been confirmed by means of the transcoronary circulation time. The transit time from left heart to coronary sinus is about seven seconds, and it decreases to three seconds following administration of nitroglycerin. In the presence of coronary artery disease, with angina pectoris, coronary blood flow changes little with nitroglycerin; coronary vascular resistance is virtually fixed, as is the myocardial extraction of oxygen and myocardial oxygen supply. The transcoronary circulation time is fixed or increased. This striking difference between the groups may be

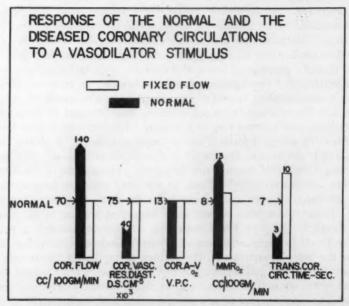


Fig. 3. Discussion in text. The direction of the arrow indicates direction of change with nitroglycerin. The figures to the left of the black column indicate resting normal values, and that at the top, the response following nitroglycerin. D.S. cm<sup>-5</sup> = dynes sec. cm<sup>-5</sup>; vpc = vol.%; MM RO<sub>2</sub> = myocardial metabolic rate for oxygen.

explained on the basis of an inadequate dilating capacity of the heart with extensive coronary artery disease. 14a, b The question may be asked, How absolute is this change? Anginal pain usually does not occur unless the disease diffusely involves the coronary tree. In 75% of cases, two of the three coronary arteries are involved. 14a, b On the other hand, we found that in some patients the coronary bed could dilate, although subnormally, following administration of nitroglycerin.

In another group of patients with angina pectoris, the measurement of coronary blood flow was repeated after a standard exercise period. In those instances where clinical pain was induced, coronary blood flow was

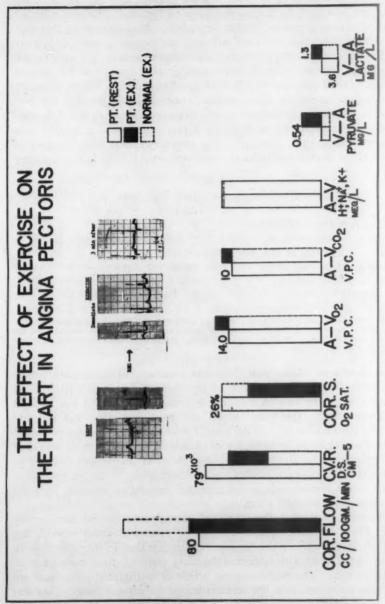


Fig. 4. Discussion in text. The electrocardiogram demonstrates the acute ST segment depression recorded following the inception of anginal pain at the time of the physiologic studies. The white columns represent the values for the normal and the augina pectoris patients at rest, indicating that all physiologic and biochemical parameters were normal at rest. The dotted dotted perform indicates the possible normal response to effort, and the black column, that in angina pectoris. The dotted values below the base line for pyruvate and lactate indicate utilization of these substances at rest; values above the base line indicate production.

found to be inadequate to demand, and an attempt to meet the need for more oxygen was made by increased oxygen extraction. This was reflected by a fall in coronary venous oxygen saturation. It is interesting that coronary venous saturation remained virtually unchanged in normal patients and in five patients who were known to have angina pectoris but who did not develop either ischemic pain or electrocardiographic changes at the time of the study. In all patients with both anginal pain and a fall in coronary venous oxygen saturation, there was an associated depression of the S-T segment in the electrocardiogram taken simultaneously with and following exercise. Figure 4 shows the findings in one patient who developed pain and electrocardiographic changes. The coronary blood flow, instead of rising on effort, was virtually fixed; there was only a 10% fall in coronary

TABLE 1
The Effect of Nitroglycerin on the Heart in Angina Pectoris (J. L.)

	Rest	NTG
Coronary flow (c.c./100 gm./min.)	81	89
Coronary resist. (d.s. cm8)	$79 \times 10^{3}$	63 × 10 <sup>3</sup> (20% decr.)
Left vent. work (Kg. M./min./M²)	4.1	3.2
Arterial pressure (mm. Hg)	138/90	107/78
Venous pressure (mm. Hg)		
Left atrium Right atrium	8 5	4

These data show a 20% decrease in coronary resistance following administration of nitroglycerin, indicating only a moderate coronary dilatation as compared to the normal. On the other hand, cardiac work, arterial pressure and filling pressures of both ventricles decreased considerably with nitroglycerin.

vascular resistance. As a result, there was a marked fall in coronary venous oxygen saturation and an increase in myocardial oxygen extraction. At the same time, there was no measurable change in hydrogen ion, sodium or potassium flux. The heart, which had been extracting and utilizing lactate and pyruvate in the resting state, the produced these substrates during exercise; this suggests the initiation of glycolysis by a very short period of tissue hypoxia. The ability of the heart to incur an oxygen debt or to maintain reactive hyperemia after an ischemic stress is as yet unknown, although recent studies indicate an increased amount of reducing enzymes in the chronically ischemic heart.

It remains to discuss the action of nitroglycerin in coronary artery disease: These studies have demonstrated no *general* coronary vasodilating effect from this drug. It has been our experience that an increase in work on effort of the heart with restricted coronary reserve, often produces myocardial ischemia. The one consistent action of nitroglycerin that was observed was a diminution in the contractility of the myocardium. This was indicated by a fall in blood pressure, a fall in cardiac output, and therefore a marked fall in cardiac work (table 1). This was accompanied also by a

decrease in pulmonary and systemic venous pressures. It is our belief that the effect of nitroglycerin on resting hemodynamics, and also its action in modifying the circulatory response to exercise, <sup>18</sup> may well play a major role in its ability to relieve anginal pain.

## SUMMARY

- 1. Studies of the coronary circulation have been carried out in 50 patients, 23 of whom had angina pectoris.
- 2. Coronary flow was shown to depend upon the need for oxygen by the heart, and this, in turn, to be related to the hemodynamic and metabolic factors of that moment.
- 3. Nitroglycerin, while causing a coronary vasodilatation in normals, failed to do so to any extent in patients with angina pectoris.
- 4. Exercise had a variable effect in patients with angina pectoris. In those with no clinical pain or electrocardiographic changes, the increase of coronary flow was adequate to the needs. In those with angina and depressed S-T segments, myocardial ischemia was evidenced by a fall in coronary venous oxygen saturation and the appearance of both lactate and pyruvate in coronary venous blood.
- 5. Nitroglycerin effects in angina pectoris are probably attributable to modification of cardiac venous return and contractility, and depression of hemodynamic change on effort.

#### ACKNOWLEDGMENTS

The authors are indebted to Dr. Albert E. Renold, through whose laboratory facilities the determinations of lactates and pyruvates were made, to Miss E. Alexanderson and Mrs. E. Hughes, for technical assistance, and to Mrs. E. Ward, for secretarial aid.

#### SUMMARIO IN INTERLINGUA

Esseva effectuate studios del circulation coronari in 50 patientes, incluse 23 con angina de pectore. Esseva monstrate que le fluxo coronari depende del requirimentos de oxygeno in le corde, e que iste requirimentos, de lor parte, es relationate a factores hemodynamic e metabolic que es simultaneemente presente. Nitroglycerina, que causa vasodilatation in subjectos normal, non exerce un tal effecto a grados significative in patientes con angina de pectore. Le effecto de exercitio in patientes con angina de pectore esseva variabile. In patientes sin dolores clinic o sin alterationes electrocardiographic, le resultante augmento del fiuxo coronari esseva adequate pro le requirimentos. In patientes con angina e depression del segmento S-T, le resultato esseva ischemia myocardial, evidentiate per un reduction del saturation coronario-venose de O<sub>2</sub> e le apparition de lactato e pyruvato in sanguine coronario-venose.

Le effectos de nitroglycerina in patientes con angina de pectore es probabilemente attribuibile a un modification del retorno cardiaco-venose, a un alteration del contractilitate del corde, e a un depression del alterationes hemodynamic causate per effortio.

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# CLINICAL MANIFESTATIONS OF PULMONARY BLASTOMYCOSIS\*

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In the 20 years that have elapsed since the classic review by Martin and Smith 10 focused attention on North American blastomycosis, numerous reports 2, 4, 9, 11, 18, 14, 15 have indicated that blastomycotic infections are not uncommon. The frequency of occurrence of such infections has probably changed very little, but the recognition of them has been increased by several factors, important among which are the greater awareness of clinicians of fungus infections in general, a wider application by clinical diagnostic laboratories of technics for the detection of fungi in material submitted for culture, and the more frequent use of special staining procedures by pathologic laboratories. At the present time the status of knowledge concerning epidemiologic, clinical and pathologic aspects of blastomycosis is incomplete and does not approach what is known about these aspects of histoplasmosis and coccidioidomycosis. It would therefore seem appropriate to record clinical experiences with blastomycotic infections, so that further knowledge may be gained. In addition, this particular summary of cases will stress the clinical aspects of pulmonary involvement in blastomycosis, since these features were prominent during the course of these infections, and also because individual patients often presented as challenging diagnostic problems.

# CASE MATERIAL

The cases in this series were collected from the University of Arkansas Medical Center and the Little Rock Veterans Administration Hospital by reviewing the charts of all hospital patients for whom the diagnosis of blastomycosis was recorded, the autopsy records, and the available records from the hospital diagnostic laboratories. Since the records of patients seen only in the Out-Patient Department were not coded, it is possible that some cases may have been missed by this process of selection. The diagnosis of blastomycosis was considered to have been confirmed when one of the following criteria was present: (1) cultural isolation of Blastomyces dermatitidis, (2) identification of the morphologically typical, doubly-contoured, singly-budding yeast form of B. dermatitidis in tissue sections obtained by biopsy or at autopsy, or (3) identification of typical blastomyces

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TABLE 1
General Characteristics of 35 Patients with Blastomycosis

оте	pee vecd in accident)  Fra TB)
Outcome	Died Improved Included Improved Included Improved Included Improved Included Improved ImproveDimental Improved ImproveDimental
Treatment	X-ray, Kil, x-ray, stil,* amphory Kil, x-ray, stil,* amphory Antibiotics Still Kil, x-ray, still Kil, x-ray, still Kil, x-ray
Duration or Follow-up	22 mos. 9 mos. 9 mos. 9 mos. 1 yrs. 1 yrs. 1 yrs. 1 yrs. 4 mos. 5 mos. 5 yrs. 2.5 yrs. 2.5 yrs. 2.5 yrs. 3 yrs. 3 yrs. 2.5 yrs. 5 mos. 1 yrs. 5 yrs. 1 yrs. 5 mos. 1 yrs. 5 mos. 6 mos. 6 mos. 2 yrs. 6 mos. 2 wrs. 6 mos. 2 yrs. 7 yrs.
Ppta.	+ 0000 + 0++ +0+0 0 0
C.F.	11:4 11:4 11:6 11:0 11:0 11:0 11:0 11:0 11:0 11:0
Skin Test	++00 +0 0000 000 0000 +000 ++ +
Organ System Involved	Skin, lungs, prostate, testis Skin, lungs, bone Skin, lungs, bone Skin, lungs, bone Skin, lungs, bone, lular node, psoas Lungs Skin, lungs, bones, lular nodes Skin, lungs, bone, general adenopathy Lungs Skin, lungs, bone, general adenopathy Lungs Skin, lungs, bone, general adenopathy Skin, lungs, bone Skin, lungs, bones Skin, lungs, bones Skin, lungs, bones Skin, lungs, kidney, tewis, spleen, nodes,
Sex	NE KREKERINGEN KEKERINGEN KEKER
Race	. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
Age	24 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
atient	407576HAMAHAQQH JAMAKAMAHACAHAM AC

\* Stil = stilbamidine or a derivative Ampho = amphotericin. in fresh preparations of body fluids or exudates, coupled with a positive serologic reaction with blastomyces antigen. Since Harris et al.<sup>6</sup> found positive blastomycin complement-fixation reactions in healthy individuals with no evidence of active blastomycosis, it was felt that a positive complement-fixation reaction alone was insufficient evidence for active blastomycosis. Two such patients were therefore eliminated, leaving a total of 35 patients for analysis. Of these, 15 have been seen personally. The first patient in whom the diagnosis was established was seen in 1939. In the period 1954–1958, blastomycosis was found in 18 individuals.

## GENERAL CHARACTERISTICS

The general composition of the patient group, whose essential features are summarized in table 1, was similar to that reported by others. There was a preponderance of males (30 males to five females). The age at the onset of the infection ranged from two to 70 years; 25 of the patients were

Table 2
Frequency of System Involvement in 35 Patients with Blastomycosis

Skin	28 (80%)
Lungs	27 (77%)
R. E. S.—nodes, spleen, liver	13 (52%)
Bones	12 (48%)
Genitourinary tract	5 (14%)
Larvnx	3 (9%)
Oropharynx	2 (6%)
Heart	2 (6%)
Meninges, pituitary, thyroid, psoas	1 each

from 20 to 59 years of age, and only two were under 10 years. Negroes were more prevalent, there being 20 Negro and 15 white patients. The occupations of the infected individuals were varied; 16 of them worked or lived on farms, seven were engaged in lumbering activities, while the others had no unusual exposure to the soil or trees. It is doubtful that much significance should be attached to either the race distribution or occupations, since these most likely simply reflect the general characteristics of the type of individuals seen in these two institutions. Of possible epidemiologic interest was the observation that all but two individuals lived in the southeastern half of Arkansas, a region bounded by the Mississippi on the east and traversed by small tributaries, and where the important occupations are farming and logging.

System Involvement: The involvement of multiple organ systems in blastomycosis is well illustrated in these patients. Indeed, only three of the 35 had disease that was localized solely to the skin or subcutaneous tissues. This incidence is somewhat lower than that in other series, 9, 12 and may well reflect the process of selection of patients. It is quite possible that some individuals with localized cutaneous blastomycosis were seen only in the clinic; such patients would not have been found in this survey. An addi-

tional four patients had pulmonary disease only, without other systems involved. Accordingly, 28 of the 35 patients had multisystem involvement. As described in other series, the organs most frequently involved were skin and subcutaneous tissues, lungs, bones, reticuloendothelial system, and genitourinary tract. The frequency of involvement is presented in table 2.

Skin Tests: Skin tests with blastomyces antigens were performed in 24 patients at some time during the course of their illness. Only six gave positive results; in two a positive reaction was obtained only on repeated testing. These results confirm the unreliability of skin testing for estab-

lishing the diagnosis of blastomycosis.3

Serology: Complement-fixation reactions of serum with blastomyces antigen were done in 19 individuals, of whom 13 gave positive reactions. Of the six individuals with negative reactions, five had active disease at the time of testing, an observation noted by others.<sup>8, 12</sup> While the data are not complete enough to allow definitive statements, it was noted that in two patients the complement-fixation reaction became negative one and two months, respectively, after therapy. Fifteen of the patients had complementfixation tests with Histoplasma capsulatum antigens. A positive reaction occurred in five, and four of these also had positive blastomycin complementfixation reactions. In four individuals the titer for histoplasma reactions was higher than the titer for blastomycin reactions, while in the other the titers were equal. Of the five patients with positive histoplasma reactions, three had positive skin test reactions to histoplasmin antigens, one had a negative skin test, and the other was not tested. In general, those patients with positive histoplasma complement-fixation reactions had only a oneor two-tube higher titer than the blastomyces complement-fixation titer. Coccidioidal complement-fixation reactions were done in six individuals; none gave positive results.

Agar-diffusion precipitin reactions, susing serum from the individual and antigens extracted from blastomyces, were performed by Dr. Douglas Heiner in 15 patients. Six had positive results. However, not all patients had active disease at the time of testing. All those with positive precipitins had active disease. Indeed, in two individuals the precipitin reaction was posi-

tive when the complement-fixation reaction was negative.

Course: The variable course of blastomycotic infections was well shown in this group. Although follow-up examinations were often sporadic and inadequate, it was observed that the individual illnesses ranged from one with a fulminant course leading to death in three months after onset, to one stretching out over at least 18 years. Of the total group, nine are known to have died (one death resulting from a car accident). The duration of illness in the known nine fatal cases ranged from three months to five years, with an average of 22 months. In contrast, other individuals were followed for seven, 10 and 18 years, respectively, and exhibited exacerbations and remissions over the years.

not vet been determined.

Therapy: Therapy for these individuals also varied considerably, and included local x-ray therapy for cutaneous lesions, potassium iodide, stilbamidine or its derivatives, 2-hydroxystilbamidine or aminostilbamidine, various antibiotics, and amphotericin. Because of the variability in the course of the infection and the often inadequate follow-up, it is difficult to determine in a critical fashion the precise efficacy of these various therapies. Thirteen patients received one of the stilbamidines in varying amounts. Nine showed some initial improvement, with relapses occurring in seven; in four patients this therapy had no discernible effect. Amphotericin has been given to 12 individuals; the results have been encouraging as concerns immediate response to therapy, but none of the patients has been observed long enough to determine the incidence of relapses after therapy. At the present time, of all the agents used, amphotericin appears to be the most effective; the optimal amount and duration of therapy with this agent have

## PULMONARY BLASTOMYCOSIS

Because pulmonary involvement was so frequent in these patients, particular attention was given to the manifestations of pulmonary blastomycosis. Of the total of 35 patients, 27 had pulmonary involvement. In four, pulmonary disease was the only manifestation of blastomycosis. The presence of pulmonary disease was determined by a combination of symptoms and the demonstration of pulmonary lesions on x-rays; all 27 individuals had abnormal chest x-rays at some time. These patients should more accurately be separated into three groups as to the etiology of their pulmonary disease. In one group, comprising 14 patients, the pulmonary disease was proved to be due to blastomycosis by identification of blastomyces in smears and cultures of sputum or lung tissue, or in tissue sections of the lungs. In a second group (five patients), the involvement was almost certainly due to blastomycosis, since other possible agents (bacterial, tuberculous, or other mycotic microorganisms) could be excluded on the basis of adequate cultures, skin tests and serologic reactions. In a final group of eight patients, the diagnosis must be considered as only presumptive, since there were insufficient cultural or immunologic data to exclude some agent other than blastomyces; in five of these patients, the pulmonary lesions healed under observation (often with therapy), suggesting that the lesions were presumably related to blastomycotic disease demonstrated elsewhere. No appreciable differences as to symptoms, physical findings or x-ray changes could be demonstrated among these three groups. Therefore, the entire group of 27 patients is considered in the following discussion.

The clinical manifestations of pulmonary blastomycosis in these patients have been analyzed in some detail to determine if any distinctive and diagnostically helpful features could be found. As shown in table 3, pulmonary involvement occurred frequently in combination with other organ system

involvement; the skin was also involved in 21 of these patients, most of whom also had other systems involved.

Pulmonary Symptoms: Sixteen individuals experienced pulmonary disease as the initial manifestation of their infection; in one the disease was found on a routine chest x-ray before symptoms appeared, while the others all had respiratory symptoms as the initial complaint. In 11 individuals, pulmonary disease occurred following some other initial manifestation; only six of these had respiratory symptoms. The symptoms experienced were: cough, nonproductive in five patients and productive in 12; chills and fever in 12; hemoptysis in 10; pleuritis in six; dyspnea in six. Such symptoms are obviously not very specific. The degree of dyspnea in these individuals was unexpected. In three, severe dyspnea caused marked restriction of activities, and moderate restriction in three others. Following therapy, the dyspnea cleared in three patients but remained unchanged in the others.

TABLE 3
Pulmonary Involvement in Blastomycosis

Total Patients	35
Pulmonary involvement Lungs only	4 27
Lungs and skin	4
Lungs, skin, other organs	17
Lungs and other organs without skin	2

Pulmonary Physical Findings: In contrast to the frequency of symptoms, physical findings were present in only 12 patients (45%). The most common finding was the presence of râles (six patients); these were usually described as coarse. Other findings included: rhonchi in two patients, pleural effusion in two, pneumothorax in two, clubbing of fingers in two, consolidation in one, and cyanosis in another. Both of the patients with clubbing had severe dyspnea; one was demonstrated to have an alveolar-capillary diffusion block by pulmonary function studies, and the other developed emphysema with a progressively declining vital capacity. It is of interest that both of the patients experiencing pneumothorax were receiving adrenocorticosteroid therapy, one for lupus erythematosus and the other for the alveolar-capillary block syndrome.

X-ray Findings: All of the 27 patients had abnormal chest x-rays. The incidence of the various types of changes is tabulated in table 4. Pulmonary calcification due to blastomycosis was not seen in this series. The most common reaction was one characterized by mottled and irregular densities of varying outlines and sizes; this has been classified as an infiltrative reaction, and was present in 21 individuals. At some time in their course, five of these individuals also showed what is classified as fibrosis, since the original infiltrate densities became smaller and strandlike in appearance. These infiltrative or fibrotic reactions had no distinctive features or locations, so that no specific diagnostic appearance could be noted.

Pleural reactions were the next most frequent roentgenographic changes seen. These occurred in 11 patients. In two, pleural effusion was confirmed by thoracentesis. In the other nine patients there was evidence of pleural thickening but not of effusion. This thickening was most often localized adjacent to areas of parenchymal involvement. Rib involvement was present in four individuals with pleural reactions, and was also present in one who had only an infiltrative reaction, without evidence of pleural disease.

Enlargement of thoracic lymph nodes was present in the x-rays of seven individuals. The adenopathy was usually not marked, and in several individuals was noted only on planigraphy. Hilar adenopathy was seen in six patients, being the only abnormality in one patient. An additional

Table 4
X-ray Findings in 27 Patients with Pulmonary Blastomycosis

Infiltrative-fibrotic	2:	(78%)
Pleural reactions	11	(78%) (41%)
Effusions	2	
Thickening	9	
Adenopathy		(26%)
Hilar	6	
Paratracheal	1	
Cavity		(11%)
Miliary reaction		(11%)
Atelectasis		(7%)
Pneumothorax		(7%)
Pneumonia	1	(4%)
Pseudocarcinoma	1	(4%)

individual presented with paratracheal adenopathy. The adenopathy was unilateral in four patients and bilateral in three. In addition to these seven patients, two were found to have distinct mediastinal adenopathy at autopsy; this had not been apparent on the chest x-rays.

Cavities were seen in three patients. All had shown infiltrative lesions prior to cavitation. In two patients, a single cavity was present. In the other patient, multiple thin-walled cavities developed in both upper lungs. An additional patient who experienced a pneumothorax was found at thoracotomy to have a large cavitary lesion which had ruptured.

Miliary pulmonary lesions occurred in three individuals. In two, miliary spread developed from previously demonstrated localized infiltrative lesions. The other patient presented initially with bilateral pleural effusions, and three days later was shown to have miliary lesions. Two of the patients were treated with amphotericin and had good regression of the miliary process.

Other roentgenographic patterns included pneumothorax in two patients, atelectasis in two, pneumonia in one, and pseudocarcinoma in another. The last's initial chest x-ray showed infiltration in the right lower lobe and a mass in the right hilum; later films revealed atelectasis of the right lower lobe. The diagnosis in this patient was readily made, since he presented

with typical cutaneous blastomycosis, and his sputum contained numerous blastomyces.

In 23 of the 27 patients, chest x-rays were repeated over variable periods of observation, ranging from three weeks to 10 years. Improvement was noted in 11 individuals; four of these were followed for less than six months, however, and relapse may have occurred later. Progression of disease was noted in 10 individuals. No change was seen in two patients who were followed less than six months. It was difficult to evaluate the role of therapy in these changes. In several individuals it was noted that lesions in the lungs regressed, but exacerbations occurred in other organ systems.

## CASE REPORTS

To present more vividly the clinical features, particularly some of the more perplexing diagnostic problems encountered, six representative patients have been selected for individual case reports.

Case 1. J. C., a 60 year old watchman, was admitted to the Little Rock Veterans Administration Hospital on January 18, 1958. One month earlier he had developed a cough which was at first productive of scant whitish sputum, and two weeks later contained flecks of blood. He felt well and had continued to work.

The patient had been admitted on three previous occasions. The first was in April, 1954, for osteoarthritis; a chest x-ray was normal. The second admission was in April, 1957, for evaluation of paroxysmal atrial tachycardia. No significant cardiovascular abnormalities were found. A chest x-ray showed an indistinct 5 cm. density in the apex of the right lower lobe; no investigation of this lesion was made. A third admission occurred from May to August, 1957, because of recurrent jaundice and abdominal pain. A cholecystectomy revealed cholelithiasis and cholecystitis. A chest x-ray in May, 1957, showed an increase in the right lung lesion; in June, 1957, this lesion had cleared somewhat, but a patchy density was now seen in the posterior basal segment of the left lower lobe. Again, no investigation of these lesions was made.

On admission in January, 1958, no significant physical findings were noted. Skin tests showed a positive histoplasmin reaction and negative reactions to blastomycin and coccidioidin. X-rays of the chest, including planigraphy, revealed an infiltration in the lateral segment of the right middle lobe; bronchograms showed obstruction of the lateral segmental bronchi in the right middle lobe, and chronic bronchitic changes in the right upper lobe and posterior basal segments of the left lower lobe. After a month's observation and therapy with antibiotics, the lesions had not changed; sputum smears and cultures had not revealed any pathogenic organisms. The patient was then advised to have surgical exploration of the pulmonary lesion because of concern about a carcinoma. Fortunately, sputum cultures finally revealed B. dermatitidis; serologic studies gave a blastomycin complement-fixation titer of 1:16 and a histoplasma titer of 1:32. The patient then-received amphotericin intravenously over a seven-week period. The cough and sputum disappeared rapidly, and at discharge in June, 1958, the pulmonary infection had shown 60% clearing. By March, 1959, the infiltrate had almost fully resolved.

Comment: This patient illustrates that blastomycotic pulmonary infections may be asymptomatic for significant periods, and that the infection may be limited solely to the lungs. He also points up the value of careful and

repeated culturing for fungi in patients with pulmonary disease of undetermined origin. The serologic results were unexpected, but it is possible that the higher histoplasma titer resulted from the antigenic stimulus of the histoplasma skin test applied earlier, as reported by Heiner.<sup>8</sup>

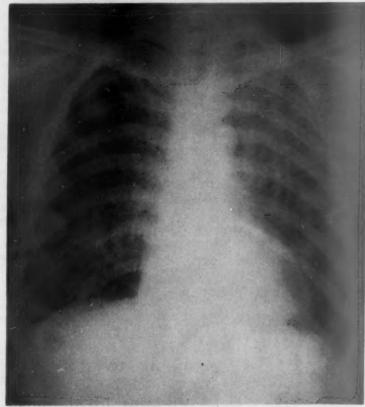


Fig. 1. Case 2. Chest x-ray four months after onset of symptoms. Note miliary lesions, small right pleural effusion and cardiomegaly.

Case 2. M. M., a 51 year old farmer, was first admitted to the University of Arkansas Medical Center on March 3, 1958. Over the preceding three months he had experienced fever, chills, fatigability, weakness, anorexia, pleuritic pain, a non-productive cough, exertional dyspnea, and a 25-pound weight loss. On physical examination the blood pressure was 130/80 mm. of Hg. The fundi contained linear hemorrhages and exudates typical of diabetic retinopathy. There were bilateral pleural effusions. The heart was normal. The liver was enlarged 6 cm. The spleen was barely palpable. The venous pressure was 72 mm. saline; circulation time, 11 seconds; vital capacity, 1.6 L. The initial chest x-ray showed only bilateral pleural effusions; three days later, however, there was a widespread, finely nodular miliary infiltrate (figure 1). Extensive laboratory studies were done. There was

a microcytic, hypochromic anemia with 8 gm.% of hemoglobin and a white blood count of 17,800, with 79% polymorphonuclear leukocytes. The urine contained 1 plus sugar and 2 plus protein. A fasting blood sugar was 145 mg.%. Renal function studies were normal. Hepatic function tests were normal save for an alkaline phosphatase of 34 King-Armstrong units and a bromsulfalein retention of 12% at 45 minutes. A liver biopsy showed some periportal fibrosis but no other changes. The

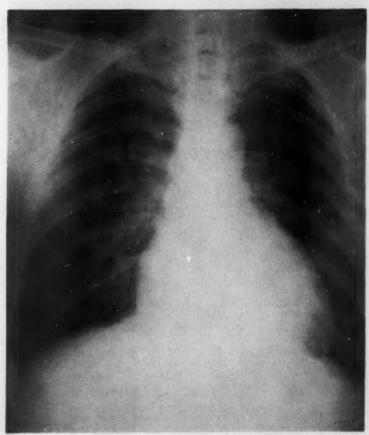


Fig. 2. Case 2. Chest x-ray 10 months after therapy with amphotericin. Note clearing of miliary process but increase in cardiomegaly.

bone marrow exhibited normoblastic hyperplasia; no granulomata were seen. Cultures of urine, sputum, gastric washings, bone marrow and pleural fluid yièlded no acid-fast organisms or fungi. A PPD #2 skin test was positive, as was the histoplasmin reaction; blastomycin and coccidioidin reactions were negative. Three L.E. preparations were negative.

Upon the demonstration of miliary pulmonary lesions and a positive PPD reaction, therapy was instituted with streptomycin, isoniazid and para-aminosalicylic acid (PAS). After two weeks there had been no clinical response. An open pleural

biopsy revealed a chronic inflammatory pleural reaction with no granuloma or giant cells; no acid-fast organisms or fungi were seen. Therapy with isoniazid and PAS was continued for an additional two weeks, without response. The patient was then

discharged on salicylates, with a tentative diagnosis of a collagen disease.

He was re-admitted on April 11, 1958, having noted continued fever and sputum, and a marked increase in the dyspnea. The physical findings were a tachycardia, a late diastolic gallop at the apex, a grade II apical systolic murmur, and hepatomegaly. The diffuse homogeneous pulmonary lesions remained as before. The sputum contained B. dermatitidis on smear on two consecutive days; cultures, however, yielded no growth. Two serum specimens, obtained a week apart, gave precipitin reactions with blastomyces antigens; complement-fixation reactions were negative. A repeat blastomycin skin test was negative. The patient was started on amphotericin intravenously, receiving a total of 1.85 gm. over a period of 34 days. Concomitantly the fever abated, except for occasional febrile reactions to the amphotericin. The dyspnea seemed to increase when amphotericin was started, and became quite marked. Although no evidence could be obtained for congestive failure, the patient was digitalized, with little benefit. After 10 days of amphotericin the dyspnea began to improve and he became ambulatory.

In June, 1958, the patient experienced a return of exertional dyspnea, and also frank congestive failure. On admission, he exhibited neck vein distention, pleural effusions, moist râles, gallop rhythm, hepatomegaly, ascites and edema. The venous pressure was 195 mm. saline; circulation time, 45 seconds. A chest x-ray showed bilateral pleural effusions and cardiomegaly; the miliary infiltrate had regressed. An electrocardiogram had large U waves and inverted T waves; serum electrolytes were all normal. On a regimen of sodium restriction, digoxin and intermittent injections of Mercuhydrin, the patient compensated quickly and was discharged after one week. There was no evidence of active pulmonary disease, and a blastomycin precipitin

reaction was negative.

The patient has since been followed in the clinic, and has continued to take digoxin for mild congestive failure. Chest x-rays have shown clearing of the pulmonary lesions and effusion (figure 2). No exacerbation of the blastomycosis has occurred in the 11 months following therapy.

Comment: This individual exhibited miliary pulmonary disease, which led to therapy for tuberculosis. Although blastomyces were not isolated in culture, the identification of them on smear, the positive precipitin reactions, and the gratifying response to amphotericin are conclusive evidence that this was miliary blastomycosis. The etiology of the congestive failure and heart disease is not certain, but may perhaps be related to the mild diabetes.

Case 3. P. H., a 49 year old plumber, was initially seen in the clinic in October, 1956. Thirty years previously he had had an episode of pneumonia, and had been investigated several times over the succeeding seven years for persistent chest x-ray abnormalities; no diagnosis had been established. A nonproductive cough persisted over the years, but he had no other complaints. In 1954 and 1956, routine chest photofluorograms had been abnormal. In October, 1955, the cough had become productive, and one month later persistent hoarseness developed. In March, 1956, his throat became sore, and dysphagia developed. A biopsy of the larynx elsewhere was said to have been nonmalignant. When first examined in October, 1956, he exhibited clubbing of fingers, erythema and edema of the oropharynx, and gray, atrophic vocal cords. A chest x-ray revealed a diffuse fine nodularity in the upper lungs and increased interstitial markings. A biopsy of the vocal cords was interpreted as "singer's node." He was then admitted for further study in January, 1957.

The vital capacity was 3.4 L. Significant laboratory data included: hemoglobin, 14.6 gm.%; serum globulins, 3.1 gm.%; serum calcium, 10.8 mg.%; serum phosphorus, 4.0 mg.%; histoplasmin skin test, positive; reactions to blastomycin and PPD #2, negative; sputum cultures for acid-fast organisms and fungi, negative. Another laryngeal biopsy showed dense scarring and granulomatous infiltration with-

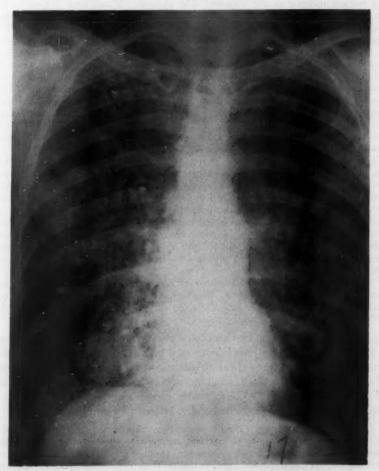


Fig. 3. Case 3. Chest x-ray after six weeks' therapy with cortisone.

Note diffuse infiltrative reaction.

out caseation. In February, 1957, a surgical biopsy of the lung revealed diffuse infiltration with epithelial cells involving the alveoli and terminal bronchioles, with focal invasion of the interstitial tissue. Analysis showed no beryllium in the lung tissue. The consensus was a granulomatous diffuse interstitial pneumonitis. The patient was discharged on no therapy.

In September, 1957, pulmonary function studies by Dr. John Pierce revealed:

inspiratory reserve, 2.375 L.; expiratory reserve, 3.009 L.; vital capacity, 5.384 L.; arterial pH, 7.42; arterial pCO<sub>2</sub>, 37 mm. Hg; arterial  $O_2$  saturation at rest, 82.3%, and after 20 minutes of breathing  $O_2$ , 104.2%. These findings were consistent with an alveolar-capillary block syndrome. Because of marked dyspnea and cyanosis, he was begun on cortisone, 200 mg. daily.

The patient returned on October 10, 1957, with increased purulent sputum and a tender ulceration at the right nostril. Examination revealed clubbing of fingers, cyanosis, scattered râles and rhonchi in the chest, and a crusted, ulcerated lesion over the right upper lip and nostril. A chest x-ray (figure 3) showed increase in the widespread infiltrate. He was initially treated with antibiotics, but no response was noted. Effusion appeared in the right knee 10 days after admission. Four days later the nasal lesion was observed to have heaped-up edges and peripheral microabscesses. Pus from the abscesses contained numerous blastomyces, as did the sputum; none were found in the joint fluid. Serologic studies gave a histoplasma complement-fixation titer of 1:16, but a negative blastomycin reaction. The precipitin reaction, however, was positive with blastomyces and negative with histoplasma. The earlier larynx biopsy was reviewed and found to contain numerous blastomyces; none could be seen in the lung biopsy. Antibiotics and steroids were discontinued, and amphotericin was begun intravenously. The skin lesion cleared promptly, sputum decreased, and after 10 days of therapy, blastomyces could no longer be found in the sputum or skin. The patient then complained of the sudden onset of right anterior pleuritic pain, which increased over the next two days. On November 11, 1957, he experienced a sudden severe increase in the dyspnea, was found to have a right pneumothorax, and died one hour later.

At autopsy, there were scattered apical adhesions. The lungs showed marked bullous emphysema, fibrosis, scattered small, thin-walled abscesses, and diffuse confluent caseous areas with surrounding consolidation. A granulomatous process had diffusely distorted the larynx, and the vocal cords were almost completely destroyed. Small abscesses were apparent in the heart, kidneys, adrenals and prostate. Blastomyces were easily seen in smears from these abscesses. Microscopically, the primary reaction was the presence of multiple abscesses containing blastomyces in the myocardium, lungs, spleen, kidneys, adrenals and prostate. The lungs were also quite fibrotic.

Comment: It is conceivable that the pulmonary blastomycosis was superimposed on some primary lung disease of unknown etiology. However, it seems equally probable that blastomycosis could account for all of the severe pulmonary symptoms. Indeed, at autopsy no evidence for any other disease could be found. This, then, is an example of the alveolar-capillary block syndrome <sup>1</sup> due to blastomycosis. The rather rapid dissemination of the infection after steroid therapy suggests that the steroid may have been responsible for the dissemination. It is also of interest to note the non-specificity of the complement-fixation reactions, whereas, in contrast, the precipitin reactions agreed with the clinical and cultural diagnosis of blastomycosis.

Case 4. R. D., a 30 year old laborer, noted onset in June, 1954, of weakness, exertional dyspnea and a cough, initially dry and later productive of yellow sputum with hemoptysis. In June, 1955, skin lesions appeared. At the Arkansas Tuberculosis Sanatorium, B. dermatitidis was found in skin scrapings and bronchial washings. Chest x-rays showed infiltrative lesions bilaterally. After some therapy with potassium iodide by his private physician, he was admitted to the University of Arkansas

Medical Center on January 25, 1956. He exhibited disseminated skin lesions, clubbing, and decreased breath sounds over the left chest. The vital capacity was 2.4 L. B. dermatitidis was grown from the sputum and skin. Blastomycin, histoplasmin and coccidioidin skin tests were all negative. The chest x-ray revealed diffuse fibrosis

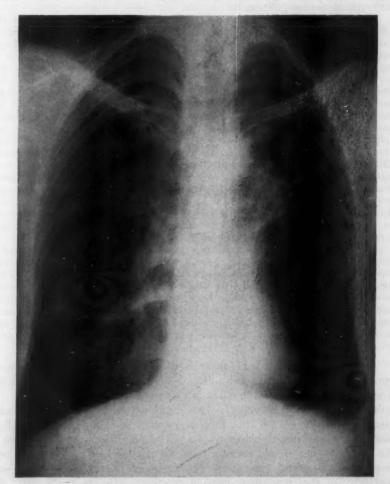


Fig. 4. Case 4. Chest x-ray one year after the third course of hydroxystilbamidine. Note prominent emphysema of the left lower lobe and bilateral fibrosis.

and reticulation, with patchy infiltrates in the right lung, shift of the mediastinum to the left, and probable left hilar adenopathy. The patient was treated with 2-hydroxystilbamidine, 225 mg. intravenously for 30 days. The skin lesions regressed promptly, but the sputum, hemoptysis and dyspnea persisted.

The patient was hospitalized again in October, 1956, because of recurrent skin lesions. There was a fungating lesion at the left nasolabial fold, with erosion of

the nasal septum. The sputum again grew blastomyces. The blastomycin complement-fixation titer was 1:16, while both histoplasma and coccidioidin reactions were negative. The chest x-ray revealed emphysema and reticular fibrosis on the left, and a patchy infiltrate in the right upper lobe. The vital capacity was 2.0 L. The patient received 55 injections of 2-hydroxystilbamidine, and healing of the skin lesions, decrease in cough, and rise in vital capacity to 2.8 L. were noted. After a month's rest he was re-admitted in January, 1957, for further therapy of the pulmonary blastomycosis, receiving 31 injections of either 2-hydroxystilbamidine or aminostilbamidine. Therapy was then stopped because of nausea, emesis and brom-sulfalein retention.

The patient has since been followed in the clinic for 2 years. He continues to have exertional dyspnea, which prevents his working. The chest x-ray (figure 4) now shows bilateral fibrosis and prominent emphysema of the left lower lobe. The vital capacity has steadily declined to 1.3 L., expelled slowly.

Comment: In this individual, pulmonary blastomycosis resulted in fibrosis and emphysema severe enough to cause respiratory functional impairment. Such a course suggests the possibility that, in some of the individuals who present with pulmonary fibrosis or emphysema of undetermined origin, the etology may have been blastomycosis. Such individuals may well have negative blastomycin skin tests or serologic tests, so that the etiology could never be proved.

Case 5. J. B., a 24 year old mechanic, experienced in November, 1956, the onset of hemoptysis, without other complaints. A chest x-ray revealed nodular densities in both upper lungs. A short course of penicillin was given by his private physician. In April, 1957, a repeat film showed bilateral cavitation. The patient had only infrequent cough and hemoptysis, and continued to work. In February, 1958, anorexia, weight loss, weakness and occasional night sweats appeared. Cough and hemoptysis occurred daily. By December, 1958, he had lost 20 pounds, and had also noted a skin lesion on the nose. He was then admitted to the Little Rock Veterans Administration Hospital. The pertinent physical findings were the obvious weight loss and a small erythematous papule on the right side of the nose. Chest x-rays (figure 5) showed multiple thin-walled cavities in the upper thirds of the lungs, with some apical pleural capping on planigraphy. The sputum contained numerous B. dermatitidis. Skin tests gave positive blastomycin, histoplasmin and tuberculin reactions. All fungus serologic reactions were negative. He was given a three-month course of amphotericin intravenously. The x-rays showed only minimal reduction in the cavities, but the sputum and hemoptysis cleared, and blastomyces could no longer be found in the sputum.

Comment: The nature of the chest x-rays suggested initially either chronic cavitary histoplasmosis <sup>5</sup> or tuberculosis. The multiplicity of the cavities and their relative thin walls are unusual in blastomycosis. It is planned to reëvaluate this patient in the future for further amphotericin therapy or possibly resectional surgery.

Case 6. M. A., a 50 year old housewife, was first admitted to the University of Arkansas Medical Center on March 28, 1956. Over the preceding eight months she had noted a weight loss of 30 pounds, weakness, pain in the upper abdomen and chest, cough and night sweats. The only positive physical finding was tenderness over the spine. Chest x-rays showed an infiltrate in the apex of the right lower lobe

and right paratracheal adenopathy. Of the extensive laboratory data, the most pertinent were: hemoglobin, 10 gm.%; tuberculin, positive; cultures of sputum, gastric washings and bone marrow, all negative for acid-fast organisms or fungi; L.E. tests, negative; muscle biopsy, normal. No definite diagnosis could be established, and she was discharged.

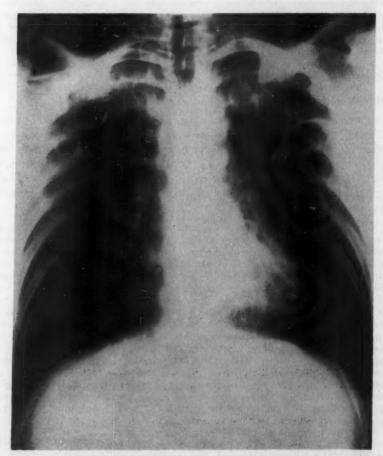


Fig. 5. Case 5. Chest tomogram two years after onset of symptoms. Note bilateral thin-walled cavities and apical pleural reaction.

The patient returned in May, 1957, because of continued weight loss, chills, fever and hemoptysis. Cardionegaly and hepatomegaly were now present. X-rays showed a persistent right lower lobe infiltrate, and also erosions of the ribs, generalized osteoporosis, and a paraspinous abscess at T 6-9. Multiple laboratory studies yielded only the additional information that she now had diabetes. No acid-fast bacilli or fungi were in the sputum or bone marrow. The patient refused to allow drainage of the paraspinous abscess. She was given insulin and then placed

on isoniazid and PAS. There was little change after two weeks, and she was discharged to continue therapy at home.

The patient was again hospitalized in September, 1957, because of continued deterioration. X-rays (figure 6) revealed further rib erosion and destruction of

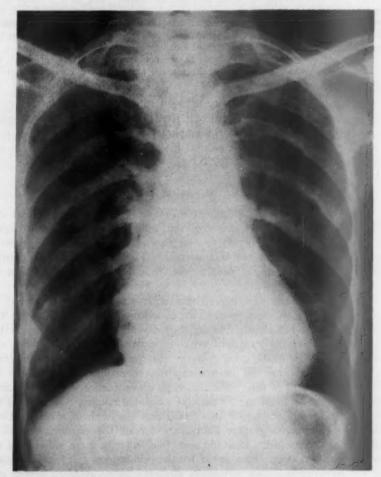


Fig. 6. Case 6. Chest x-ray fwo years after onset of symptoms. Note erosion of inferior borders of ribs, indistinct infiltrate in right upper lung, and cardiomegaly.

T 8-9 vertebrae. At this time, B. dermatitidis was seen on three consecutive days in the sputum, but cultures were negative. The blastomycin complement-fixation titer was 1:8; histoplasmin reaction, negative. A blastomycin skin test was negative. The patient then received amphotericin intravenously over a three-week period. Fever disappeared, blastomyces were no longer seen in the sputum, and the blastomycin complement-fixation became negative.

After discharge, the patient improved slightly for a short time, but she was re-admitted in February, 1958, with fever and hemoptysis. No fungi or acid-fast bacilli could be found in the sputum. X-rays showed definite healing of the ribs and vertebrae, but there was a pneumonic process in the right lower lobe. Following vigorous penicillin therapy the fever and sputum abated. The patient finally consented to surgical exploration of the paraspinous abscess. No pus was found, but there was a severe, nonspecific inflammatory response involving the vertebrae, pleura and soft tissues. No fungi or acid-fast bacilli could be seen in or grown from the tissues. The patient improved and gained weight, and was discharged.

Since then, progressive improvement has been observed. By October, 1958, the patient was asymptomatic, had gained 30 pounds, and exhibited continued healing

of the spine and right lower lobe infiltrate.

Comment: The close similarity between tuberculosis and blastomycosis is again emphasized by this patient. It seems likely that the slow but gratifying improvement was due to the amphotericin, but it is recognized that it may also have reflected the natural history of blastomycotic infections, which may regress spontaneously.<sup>2, 9, 14</sup>

### DISCUSSION

This group of patients exhibited the same general characteristics described by others. The frequency of skin and lung involvement is again emphasized, but it is important to note that any system may be involved during the dissemination of blastomycosis. The sparing of the gastrointestinal tract, excluding the oropharynx, has also been prominent in all series reported.

The presently reported experiences with pulmonary involvement in blastomycosis give strong support to the concept, advocated by Schwarz and Baum, 11 that the initial infection in blastomycosis usually occurs via the lungs. Pulmonary blastomycosis without apparent disease elsewhere was found in four individuals, good evidence that primary pulmonary infection can occur. In addition, 16 patients experienced respiratory disease as the initial manifestation of their infection, with dissemination elsewhere occurring later. While 12 of the 35 patients exhibited cutaneous lesions as the initial clinical manifestation, it was found that six of them, when first examined, had roentgenographic pulmonary lesions the duration of which could not be determined. It would seem likely that in these individuals the pulmonary infection may have antedated the skin lesions. It was also noted that the pulmonary disease originally apparent by x-ray often healed and left no visible abnormalities.9 Accordingly, it is possible that even those patients without obvious pulmonary disease may well have had at some time prior to the appearance of lesions elsewhere an asymptomatic pulmonary infection that left no residuals.

As to the clinical manifestations of pulmonary blastomycosis, there are obviously no specific diagnostic features. The physical findings in the lungs were unimpressive and not distinctive. None of the symptoms was unique.

Hemoptysis was relatively frequent, as reported by Cherniss and Waisbren.<sup>2</sup> One feature not stressed in other series was the significant dyspnea experienced by six patients. In one, pulmonary function and arterial blood gas studies indicated oxygen desaturation, most likely on the basis of impaired diffusion across the alveolar-capillary wall. This type of interference with respiratory function would be quite consistent with the granulomatous inflammatory reaction characteristic of blastomycosis, and corresponds to that described in tuberculosis, histoplasmosis, sarcoidosis, etc.<sup>1</sup> In another individual, significant dyspnea resulted from fibrosis and emphysema that developed after therapy.

The roentgenographic features conformed generally to patterns previously described by Hawley and Felson. The one noted most frequently was a nonspecific inflammatory pattern, but the variations were wide, from a single cavity to miliary reactions. While no single feature was diagnostic of blastomycosis, the combination of a parenchymal lesion plus pleural involvement was frequent enough to be helpful in suggesting the consideration of blastomycosis. Rib involvement would further suggest this. Hilar adenopathy occurs, but may not be impressive and is not specific. The absence of calcification was striking, as reported by others. Because of the nonspecificity of the pulmonary x-rays, the possibility of blastomycosis should be considered in any individual with a pulmonary lesion of undetermined origin.

These patients with blastomycosis were often treated initially for some other disease, most frequently tuberculosis. This differential is often difficult to establish, particularly when the individual does not present with typical cutaneous lesions, or does not have blastomyces in smears of fluid or sputum. However, in a patient with clinical manifestations suggesting tuberculosis, if the tuberculin reaction is negative and acid-fast bacilli cannot be found, the possibility of blastomycosis should be considered. Other mistaken initial impressions included bacterial pneumonia, collagen disease, and carcinoma of the lung. This confusion serves to emphasize the variations in the clinical manifestations of blastomycosis, and points out that blastomycosis should be considered in any perplexing pulmonary disease, even in the absence of the typical involvement of the skin and bones.

#### SUMMARY

A series of 35 patients with blastomycosis has been reviewed. Disseminated lesions occurred in 28 patients, three exhibited cutaneous lesions only, and four had only pulmonary blastomycosis. Since pulmonary involvement was found in 27 individuals, particular analysis was made of the clinical manifestations of pulmonary blastomycosis. Symptoms included cough, sputum, fever, chills, hemoptysis, significant dyspnea and pleuritis. Physical findings were not impressive; however, free pleural effusions and pneumothorax were seen. Roentgenographic features similarly were not

specific; the pattern found most frequently was one showing an infiltrative or fibrotic reaction, with pleural reactions and thoracic adenopathy occurring often. Infrequent patterns included cavities, miliary lesions, pneumonia, and an appearance suggestive of bronchogenic carcinoma.

No specifically diagnostic clinical pattern could be established for pulmonary blastomycosis. The occurrence of parenchymal pulmonary disease, in association with cutaneous, pleural, bone or thoracic nodal involvement, should strongly suggest the possibility of blastomycosis. However, because of the extremely varied clinical manifestations of pulmonary blastomycosis, this diagnosis should be considered in any pulmonary disease of undetermined origin.

#### SUMMARIO IN INTERLINGUA

Es presentate un revista del casos de 35 patientes con blastomycosis vidite al Centro Medical del Universitate Arkansas e al Hospital Little Rock del Administration de Veteranos. Le majoritate del patientes esseva masculos de etates de inter 20 e 59 annos. Multiple systemas organic esseva afficite in 28 casos. Le systemas afficite le plus frequentemente esseva pelle e histos subcutanee, pulmones, ossos, organos reticuloendothelial, e vias genito-urinari. Tres patientes habeva lesiones exclusivemente cutanee, quatro habeva lesiones exclusivemente pulmonar. Inter le patientes assi testate, solmente 25% habeva reactiones positive in le test cutanee a blastomycina, 69% habeva reactiones positive in le test de fixation de complemento a blastomycina, e 40% habeva reactiones positive in le test a precipitina in gel agar. Le curso e le duration del infectiones esseva multo variabile. In dece casos le morte del patiente es cognoscite, occurrente a intervallos de inter tres menses e cinque annos post le declaration del morbo. Altere patientes remaneva sub observation consecutori durante periodos de inter septe e 18 annos e exhibiva exacerbationes e remissiones in le curso del tempore. Le effectos de varie agentes therapeutic esseva difficile a evalutar, frequentemente a causa del inadequatia del examines consecutori. Stilbamidina o su derivatos esseva benefic in certe casos. Plus recentemente, amphotericina ha effectuate incoragiante remissiones in 12 patientes, sed observationes additional es necessari in iste casos.

Affectiones pulmonar occurreva in 27 patientes e esseva le manifestation initial in 16. Le symptomas includeva tusse, algor e febre, hemoptysis, grados significative de dyspnea, e pleuritis. Le constatationes physic esseva relativemente sparse: Effusion pleural e pneumothorace esseva vidite in certe casos. Alterationes roentgenographic esseva vidite in omne le 27 casos. Le configuration vidite le plus frequentemente esseva un non-specific reaction infiltrative o fibrose. Affection pleural esseva commun, usualmente manifeste in spissification pleural, in multe casos adjacente a un affection parenchymal. Adenopathia thoracic etiam occurreva sed rarmente in forma prominente. Le reactiones de basse frequentia includeva cavitation, lesiones miliari, pneumonia, e un aspecto suggerente carcinoma bronchogene. Es opinate que iste analyse del affection pulmonar supporta le conception que le infection initial in blastomycosis occurre usualmente via le pulmones ab ubi illo es disseminate subsequentemente.

Nulle specific schema clinic poteva esser establite pro blastomycosis pulmonar. Morbo parenchymal del pulmones in association con nodal affectiones cutanee, pleural, ossee, o thoracic debe esser interpretate como un forte indication del possibilitate de presentia de blastomycosis. De facto, iste possibilitate debe esser prendite in consideration in le studio de omne caso de morbo pulmonar de origine indeterminate.

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# PULMONARY ALVEOLAR PROTEINOSIS: REPORT OF THREE CASES\*

By Joseph C. Sieracki, M.D., Robert C. Horn, Jr., M.D., Detroit, Michigan, and SAUL KAY, M.D., Richmond, Virginia

Pulmonary alveolar proteinosis, a chronic disease of the lungs of unknown etiology, was recently described as a new entity by Rosen et al.1 Although the histologic findings are characteristic, the clinical course is variable. Inasmuch as this is apparently a new disease and, thus far, only Rosen's report has called attention to it, we are recording our experience with three cases.

#### CASE REPORTS

Case 1. A 31 year old white male entered Henry Ford Hospital on December 27, 1957, for study. Three months earlier he had noted mild dyspnea on climbing stairs which he did not consider to be disabling. Two months before admission he had been hospitalized elsewhere for an acute, febrile, "flulike" illness. He had a mild chronic cough. X-ray findings led to a working clinical diagnosis of sarcoidosis. Right scalene and left supraclavicular lymph node biopsy was performed.

The past medical history was noncontributory. The patient was known to have had a negative chest x-ray in 1949. At various times he had lived both in the San

Joaquin Valley and in southern Ohio.

The patient had worked for a chemical firm for seven years, the last four as a mechanical engineer in a pilot plant, working with various materials as tile fillers. These materials included barium, cadmium, asbestos, sand and, for the most recent 18-month period, newly synthesized chlorinated resins. He worked in an atmosphere of considerable dust and fumes. The work situation was subjected to toxicologic study, and all materials that might have been suspect as occupational hazards, except for the resins, were exonerated.

Physical examination revealed acne and minimal restriction of motion of the thoracic cage. There were no other positive findings. Laboratory data included: hemoglobin, 17 gm.%; hematocrit, 49%; erythrocyte sedimentation rate, 32 mm. in one hour. The urine contained moderate numbers of white blood cells. The total serum protein was 7.5 gm.%, partitioned as follows: albumin, 42%; α globulin, 7%; α2, 15%; β, 16%; γ globulin, 21%. Blood sugar, nonprotein nitrogen, calcium, phosphorus and alkaline phosphatase levels were within normal limits. The serologic test for syphilis was negative. Cultures of sputum were negative for acid-fast bacilli and fungi. Pulmonary function tests showed slight reduction in the total and maximal breathing capacity, without evidence of airway obstruction. This was interpreted as consistent with diffuse intrapulmonary fibrosis. X-ray of the chest revealed diffuse nodular fibrotic changes involving the most proximal portions of both lung fields, interpreted as consistent with pneumoconiosis or sarcoid (figure 1A). Histoplasmin, coccidioidin and tuberculin skin tests were all negative.

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January 2, 1958, lung biopsy was carried out. The left upper lobe and lingula were noted to be firmer than normal. Dilated superficial lymphatics and superficial yellow spots approximately 2 mm. in diameter were described on the pleural surface.

Postoperatively the patient was treated with prednisone. The initial dosage was

30 mg. per day; this was gradually reduced over a 10-week period.

On January 30, 1958, Candida albicans was cultured from the sputum. This was not regarded as significant. In February, some resolution of the infiltrate was noted

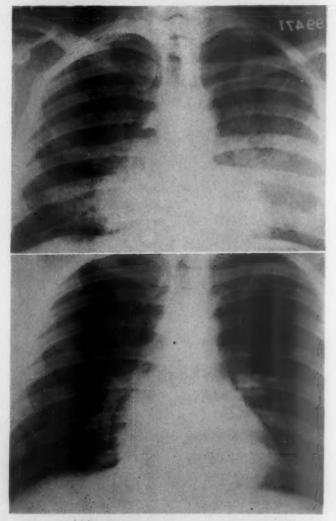


Fig. 1. Case 1. A. (above) Roentgenogram taken on December 27, 1957, prior to biopsy. B. (below) Roentgenogram eight months later, showing almost complete resolution of the process, especially marked in the left lower lung field.

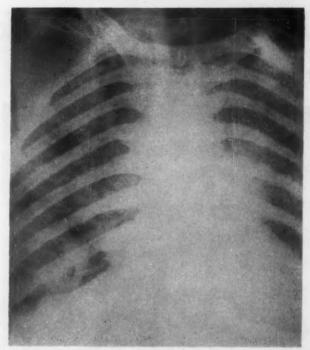
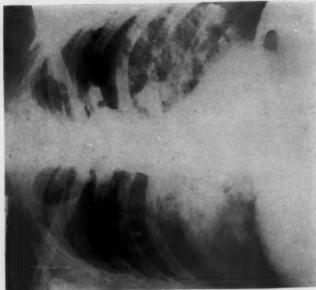
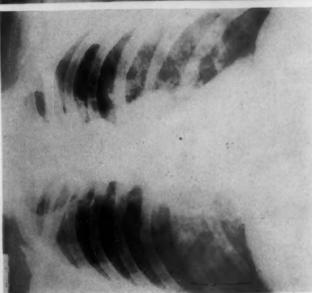


Fig. 2A. Case 2. Roentgenogram taken October 29, 1957, showing diffuse involvement of both lungs.



Fig. 2B. Case 2. Gross photograph of biopsy specimen, showing areas of consolidation and microcyst formation.





Case 3. A. (1eft) Roentgenogram taken during original illness in December, 1955. B. (right) Roentgenogram taken September 5, 1957, 21 months later, showing no significant change. F1G. 3.

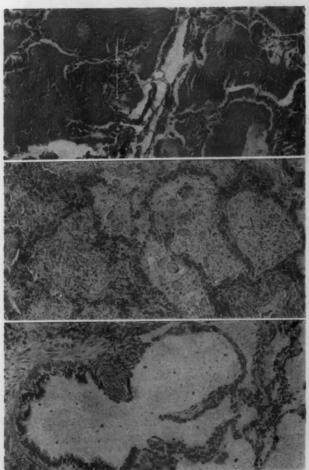


Fig. 4. A. Case 1 (left) Bronchiole, alveolar duct and alveoli filled with proteinaceous material and rounded bodies. B. Case 2 (center) Alveoli distended with same type of material as case 1, but including many acicular spaces (cholesterol clefts). The intra-alveolar material has a flocular appearance of c. Case 3 (right) Alveoli showing changes similar to A and B. Note the increased number of "septal cells" near the center and left lower corner. Except for these areas, the alveolar walls in all cases are thin. H. & E. × 115.

on x-ray examination, and by August 9, 1958, the left lung appeared to be entirely clear (figure 1B). There was progressive improvement in the maximal breathing

Biopsy Findings: The alveoli in the involved area were filled with a deeply eosinophilic material which, for the most part, was granular and floccular but included acicular spaces and rounded bodies of apparently greater density (figures 4A and 7A). The latter varied in size. This material was periodic-acid-Schiff positive, the rounded bodies being more intensely so than was the amorphous material (figure 7B). No mucicarminophilic material was present. There were no inflammatory



Fig. 5. Case 2. An expanded view to show the quality and extent of involvement in some areas. H. & E. × 115.

changes, and the pulmonary structure was essentially intact. In areas the cells lining the alveolar septa were multilayered, apparently as a result of proliferation. Some small bronchi and bronchioles showed striking muscular thickening and contraction, with narrowing of the lumen. Other special stains and histochemical studies failed to characterize the intra-alveolar material further, or to demonstrate any additional changes. Study of the sections of the lymph nodes biopsied before the patient's Henry Ford Hospital admission showed small amounts of granular and floccular periodic-acid-Schiff (PAS)-positive material, like that in the lung, in phagocytes in the peripheral sinusoids, as well as free in the stroma.

Case 2. The patient was a 35 year old white male at the time of his first admission to Henry Ford Hospital on July 24, 1958. Nine months earlier he had been hospitalized for two months for an acute respiratory illness diagnosed as bilateral pneumonia and characterized by marked cyanosis and dyspnea. No significant micro-

organisms were isolated, and there was no apparent response to a wide variety of antibiotics. Improvement was slow and gradual, concomitant with treatment with postassium iodide. One month after discharge (and six months before his Henry Ford Hospital admission) the patient had first experienced hemoptysis. This was followed by progressive cough, increasing blood-streaking of sputum, and some shortness of breath on exertion. He gained 50 pounds.

The patient had worked as a polisher of steel parts for the last 10 years.

The positive physical findings included obesity, clubbing of the fingers, diminished expansion of the chest, bronchial breath sounds, and coarse and fine râles at the right base and some fine râles anteriorly on the left.

Laboratory studies included: hemoglobin, 15.7 gm.%; white blood cell count, 10,100/cu. mm.; hematocrit, 57%. Total serum protein was 7.9 gm.%, partitioned as follows: albumin, 59%;  $\alpha_1$  globulin, 4%,  $\alpha_2$ , 8%;  $\beta$ , 10%;  $\gamma$  globulin, 19%. Serologic tests for syphilis and urine and stool examinations were negative. Erythrocyte sedimentation rate, calcium, phosphorus, alkaline phosphatase and liver function studies were within normal limits. Cultures of the lung as well as of the sputum were negative for fungi and acid-fast bacilli.

Pulmonary function studies revealed reduced vital capacity and maximal breathing capacity but a relatively normal three-second vital capacity. There was a slight reduction in arterial oxygen saturation with a further fall after exercise. Carbon dioxide tension and ventilatory studies were normal. These data were interpreted to indicate a diffusion defect or alveolar-capillary block.

X-ray examination of the chest at the onset of illness showed extensive parenchymal infiltrative disease (figure 2A).

Tuberculin, coccidioidin, mumps, monilia, blastomycin and histoplasmin skin tests were negative.

Lung biopsy was performed on July 31. The lung appeared to be underaerated. Postoperatively there was some subcutaneous emphysema.

Steroids proved to be of no benefit, but intermittent positive pressure breathing and Isuprel were of some help. The proteinolytic enzyme Tryptar was given by aerosol, 45,000 units three times a day. Although the patient raised considerable sputum, objective improvement was not observed in the radiographic appearance or pulmonary function studies.

Following discharge after 25 days, the patient moved from this area and we have not been in contact with him since.

Pathologic Examination: The segment of lung removed measured 2 by 2 by 1 cm. It was quite firm. The pleural surface appeared to be normal, but the cut surface revealed patchy, gray-yellow areas of consolidation within which tiny, cystlike spaces could be seen (figure 2B). The microscopic appearance did not differ from that of the other two cases (figures 4B and 5). A small amount of lipid was demonstrated in the intra-alveolar material with Flaming Red and Sudan III stains.

Case 3.\* The patient was a 57 year old white male dentist first admitted to the Medical College of Virginia Hospital on January 20, 1957. Approximately two years before admission he had noted exacerbation of a chronic cough of many years' duration. X-rays 13 months before admission revealed diffuse densities of both lung fields, considered to be consistent with sarcoidosis (figure 3A). A tuberculin skin test was positive, but repeated sputum studies were negative for acid-fast bacilli. Bronchoscopy and biopsy one year before admission had been negative. The patient had noted mild increasing shortness of breath on exertion, but had attributed this to advancing age.

The past, family and personal medical histories were noncontributory.

\*We are indebted to Dr. George A. Welchons for permission to include the data regarding this patient.

The only positive physical findings were: fine, moist râles heard anteriorly and posteriorly over both lung bases, a liver edge palpable 5 cm. below the right costal margin, and an enlarged right submaxillary salivary gland.

Laboratory Data: Hemoglobin, 17.2 gm.%; red blood cell count, 5,400,000/cu. mm.; white blood cell count, 7,600/cu. mm. Bromsulfalein retention, 7% at one

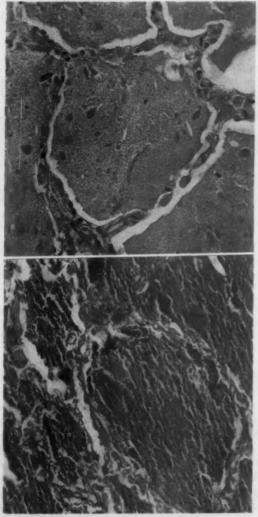


Fig. 6. Case 3. A. (above) Higher magnification to show the character of the material within the alveoli. The dark masses within the thin alveolar capillaries are red blood cells. Note the numerous acicular spaces, which were not so apparent at lower magnification (figure 4 C). Azure eosinate × 300. B. (below) The PAS-positive masses and protein-aceous material within the alveoli are much less homogeneous in PAS preparations. PAS reaction × 300.

hour. Serum proteins, 6.6 gm.%; albumin, 4.2; globulin, 2.4. Bilirubin: direct, 0.05; total, 0.1 mg.%; thymol turbidity, 3 units. Erythrocyte sedimentation rate, 16 mm. in one hour. Hematocrit, 47%. Cholesterol: total, 236 mg.%; esters, 70%. Urine, negative except for numerous white blood cells. *Candida albicans* was cultured from the sputum, but numerous specimens were negative for acid-fast bacilli.

Special Studies: Arterial oxygen saturation: 91% at rest, 94% after exercise. Arterial carbon dioxide concentration: 25 mEq. at rest, 24 after exercise. Vital capacity: 4.19 L.; after Isuprel, 4.12 L. (116.3% and 114.5%, respectively, of predicted normals). Maximal breathing capacity: 101 L. per minute; after Isuprel, 121 (99.4% and 119.3%, respectively, of predicted normals). Electrocardiogram was normal.

On January 22, 1957, the submaxillary gland was biopsied, and a report of mixed tumor was returned. The following day a biopsy of the lingula of the left lung was performed. The postoperative course was uneventful, and the patient was discharged on January 31.

X-ray examination on September 5, 1957, revealed fine linear and nodular densities in the middle third of each lung field, with prominence of both hilar areas (figure 3B). There was little change from the examination of December, 1955. Other examinations revealed normal bony structure of the hands and normal swallowing function.

A year later the patient was admitted to the Mayo Clinic, his dyspnea having progressed. On February 5, 1958, scalene lymph node biopsy was carried out but no lesion was recognized. This was followed by biopsy of the right lung.\* Diffuse deep induration was noted, especially of the upper lobe. Bacteriologic studies were negative. The patient was discharged on February 11, 1958. At present he is working at his profession, with little disability.

Biopsy Findings: The histologic findings in the left lung biopsy at the Medical College of Virginia and in the right lung biopsy at the Mayo Clinic were essentially similar, and did not differ significantly from those of case 1 (figures 4C and 6). Fat stains showed minimal amounts of lipid. These biopsies included some uninvolved pulmonary parenchyma, from which the diseased tissue was sharply demarcated. We were unable to recognize any features which we could interpret as evidences of either progression or regression in the one-year interval between the two biopsies. No abnormality was recognized in the scalene lymph nodes.

#### DISCUSSION

The histologic findings in our cases are similar to those described in Rosen's original report, consisting in the characteristic or fully formed lesions primarily of the intra-alveolar deposition of granular and amorphous eosinophilic material. This material was found in all the air spaces distal to and including the respiratory bronchioles. Acicular clefts were present within the deposit. This uniform picture with minimal inflammation was so striking that it lends weight to the hypothesis that pulmonary alveolar proteinosis is a new disease, rather than an old one that has escaped detection until recently. The eosinophilic deposit of this disease is periodic-acid-Schiff-positive but mucicarmine-negative. As reported by Rosen et al., it appears to be more granular in PAS preparations than in sections stained with hematoxylin and eosin. We also observed the "starchlike bodies,"

<sup>\*</sup>We are indebted to Dr. Lewis B. Woolner, Surgical Pathologist of the Mayo Clinic, for the opportunity to study this material.

the refractile crystals and the septal cell proliferation. Little lipid could be demonstrated by various staining technics, although Rosen reported from five to seven times the normal amount of lipid, as determined chemically.

Imprints made from the unfixed tissue of case 1 revealed a surprisingly large number of cells, many of which were actively phagocytic (figure 7). Septal cells were present in sheets, and occasional multinucleated forms were seen. The cytoplasmic granules were more intensely PAS-positive than was the proteinaceous intra-alveolar material. They bore a close resemblance to the PAS-positive macrophages in the lymph nodes. The large

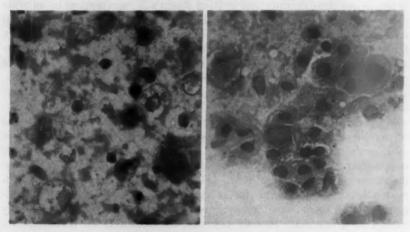


Fig. 7. Case 1. A. (left) Imprint showing many degenerated cells, some with vacuolated cytoplasm. The dark rounded mass in right lower corner is similar to those seen in sections. Leishman's stain  $\times$  980. B. (right) Imprint showing PAS-positive cells and a rounded body. These probably represent desquamated "septal cells." PAS reaction  $\times$  980.

focal deposits of crystals which displayed Maltese crosses (? Russell bodies) under polarized light also seem noteworthy, particularly in view of the small number of plasma cells seen in both the sections and the imprints. Similar crystals were not seen in the lymph nodes.

Physical studies were carried out on the biopsy material in case 1 by Mr. Jonathan Parsons, of the Physics Department of the Edsel B. Ford Institute for Medical Research. His report is as follows: "X-ray diffraction on fresh tissue showed no crystalline pattern—the ashed specimen gave a strong crystalline pattern of sodium phosphate and an unidentified secondary component. No silicates were present. Spectrographic analysis indicated the presence of the following elements (listed in order of greatest prevalence): phosphorus, sodium, calcium and magnesium."

This study, together with the striking occupational history in this case, makes the hypothesis of a chemical pneumonia or pneumoconiosis highly attractive. However, one component of the diseased lung tissue remains

unidentified, and no corresponding history can be elicited in the other two cases. Similarly, Rosen and his co-authors were unable to pinpoint any feature common to all, or even most, of the cases in their series that might have suggested an etiology. Perhaps a similar histopathologic picture may be produced by a variety of causal agents. We agree with Rosen et al. that pneumocystis carinii infections can be ruled out, and that the Grocott stain is particularly helpful in this respect.

The initial complaints of our patients were those of dyspnea and cough, as they were in most of the cases in the original report. The onset of disease in two of our three patients, and in 10 of Rosen's 27, was marked by an acute respiratory tract illness. Males predominated two-to-one in the original series, and all three of our patients were males. The disproportion between the symptoms and the extensive bilateral pulmonary involvement demonstrable by roentgenograms in early or mild cases is noteworthy in two of our cases, as well as in many of Rosen's. In cases 1 and 3 reported here, atypical sarcoidosis without hilar lymphadenopathy was suggested as a possibility by the radiologist, and case 2 was considered to be atypical pulmonary edema on the basis of the original roentgenograms. In only one of our patients (case 2) was the degree of disability great, whereas eight of Rosen's cases terminated fatally. One patient (case 1) showed great improvement, as judged by radiographic study, but he had virtually no limitation of activity at any time. The improvement coincided with prednisone therapy. There was similar improvement in the x-ray findings concomitant with prednisone therapy in one of Rosen's cases, but without any change in symptoms. In only one case did Rosen et al. note any real improvement.

## SUMMARY

Three new cases of pulmonary alveolar proteinosis are reported. The histologic findings in biopsy material from the lungs are essentially identical and do not differ from those originally detailed by Rosen et al. The granular and crystalline inclusions in the proteinaceous intra-alveolar deposit that characterizes the disease are emphasized. Periodic-acid-Schiff-positive material, similar to the amorphous intrapulmonary deposit, was found in phagocytes in the supraclavicular lymph nodes of case 1.

This study supports the concept that pulmonary alveolar proteinosis is a new disease, but a factor or factors common to all, or most, of the cases that might point to etiologic possibilities remain unidentified.

#### SUMMARIO IN INTERLINGUA

Es reportate tres nove casos de proteinosis pulmono-alveolar. Tusse e dyspnea esseva le major gravamines de iste patientes. In duo del tres casos, le declaration del morbo esseva marcate per le signos e symptomas de un acute morbo respiratori. Le roentgenogrammas obtenite durante le phases initial del morbo suggereva atypic sarcoidosis sin affection de hilar nodos lymphatic o atypic edema pulmonar. In duo

del patientes le grado de invaliditate non esseva marcate, ben que le roentgenogrammas demonstrava extense affection pulmonar bilateral. Iste discrepantia inter le signos e symptomas clinic e le constatationes roentgenographic es possibilemente un indicio in le diagnose clinic del morbo. Studios laboratorial non contribueva al clarification del diagnose. In omne le casos, le diagnose esseva establite super le base de biopsias pulmonar. Ab le puncto de vista histopathologic, le constatationes esseva simile in le tres casos. Characteristicamente le lesiones exhibiva deposition de un granulo-amorphe materia de comportamento eosinophile in le spatios aeree. Iste materia es positive pro acido periodic de Schiff. Iste e altere constatationes histologic es si frappante e si uniforme que le hypothese gania in probabilitate que il se tracta hic de un nove morbo plus tosto que de un morbo que escappava usque nunc al detection. Le etiologia de proteinosis pulmono-alveolar remane obscur.

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# ISOSENSITIZATION TO A NEW BLOOD FACTOR. RhD, WITH SPECIAL REFERENCE TO ITS CLINICAL IMPORTANCE \*

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IMMEDIATELY following the announcement of the discovery of the Rh factor by Landsteiner and Wiener two decades ago came the demonstration of the role of Rh sensitization in the causation of hemolytic transfusion reactions,2 and in the pathogenesis of erythroblastosis fetalis.<sup>3</sup> As a result, routine Rh testing has become an essential part of the management of expectant mothers and of the selection of donors for blood transfusion. Study of serums from isosensitized patients has demonstrated that while the bulk of clinical problems are caused by sensitization to the originally described rhesus factor, now designated Rhot, many other blood factors belonging to a number of different blood group systems at times play a role.<sup>4</sup> Of these, the most interesting are the blood factors which are related to factor Rh, and which, together with Rho, determine the Rh-Hr blood group system. 5,6 At present, it is known that many Rh factors exist, namely, Rho, rh', rh", rh, and others, together with certain reciprocally related Hr factors, hr', hr'', hr and hr and sensitization to any of these blood factors can give rise to clinical problems; in fact, it was a clinical problem which originally led to the discovery of each of these blood factors. Of the various blood factors of the Rh-Hr system, blood factor Rh, is by far the most antigenic, as evidenced by the fact that most of the clinical problems arise from Rh, sensitization. Thus, the Rh, factor appears to hold a special position within the Rh-Hr system, and for this reason the symbol for that factor has been assigned a capital "R" in order to set it apart from the other Rh-Hr factors.

It is evident that while the Rho-negative individual is in greatest

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† In this paper, in conformity with the recommendation of the Committee on Medicolegal Pathology of the Appairs of Medical Association, supplied for against incommence and phenetypes and the Committee on Medicolegal Pathology of the Committee

Problems of the American Medical Association, symbols for agglutinogens and phenotypes are printed in regular type, symbols for blood factors and their corresponding antibodies in **bold-face** type, while symbols for genes and genotypes are printed in *italics*.

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jeopardy of becoming isosensitized, the Rho-positive patient is not immune, because he can be sensitized to any of the numerous other Rh-Hr factors that may be lacking from his red cells. Of special interest is the recent discovery that occasionally when Rh positive individuals become isosensitized their serums may be found to contain antibodies seemingly identical with anti-Rh, in specificity. This seeming paradox has been explained by the demonstration that the antibodies in question. while simulating anti-Rh, are actually not identical with anti-Rh, in specificity, since they do not react with the individual's own Rh-positive cells nor with cells of certain other rare Rh-positive individuals. Moreover, when the serums from different cases of this nature were compared. it was found that, in general, the antibodies differed not only from anti-Rh, but also from one another in specificity. It appears, therefore, that in "standard" Rh-positive blood cells there are associated with blood factor Rh, many other blood factors, RhA, RhB, RhC, etc. In certain rare Rh-positive individuals, one or more of these blood factors may be lacking, and if such a person becomes isosensitized, the resulting antibody anti-RhA, or anti-RhB, or anti-RhC, etc., as the case may be, simulates anti-Rh, in specificity for the reasons already given.

The first case of this nature was reported by Shapiro.8 namely, an Rho-positive\* patient with a potent antibody in her serum paralleling anti-Rho in specificity. Unfortunately, the serum of this patient is no longer available for study. Later, Argall<sup>9</sup> reported a similar case, and he too did not assign any special designation to the antibody in his patient's serum. More recently, Wiener, Geiger and Gordon<sup>10</sup> reported a case of erythroblastosis in a type Rhirh baby with a type Rhirh mother who had antibodies in her serum paralleling anti-Rh, in specificity. Closer study showed, however, that the antibodies in question were different not only from anti-Rh, but also from the antibodies of Argall's patient, and also of a case reported by Rosenfield et al. 16 at about the same time. To the antibody in their patient's serum. Wiener et al. have assigned the symbol anti-RhA, and the blood factor detected by this serum is therefore Rh<sup>A</sup>. Unger, Wiener and Weiner<sup>11</sup> reported a hemolytic transfusion reaction in an Rh-positive patient sensitized to Rh-positive blood. The antibody in their patient's serum proved to be different from anti-RhA and has been assigned the symbol anti-RhB. with the corresponding factor Rh<sup>B</sup>. Unger and Wiener<sup>12</sup> also reported a case of subclinical erythroblastosis in a pair of fraternal twins caused by isosensitization to Rh-positive blood. Since the antibody responsible proved to be different not only from anti-Rho but also from anti-Rho and anti-RhB, it has been assigned the symbol anti-RhC, and to the corresponding factor the symbol Rh<sup>C</sup>.

<sup>\* %</sup>ho-positive blood (or Rho variant blood) is defined as blood which is not clumped, or is only weakly clumped, in saline medium by agglutinating (or bivalent) anti-Rho serum, but is clumped by blocking (or univalent) anti-Rho serum by the conglutination, antiglobulin and/or proteolytic enzyme technics.

The purpose of the present paper is to report still another case of erythroblastosis fetalis caused by sensitization to a blood factor related to but different from  $\mathbf{Rh_o}$ ,  $\mathbf{Rh^A}$ ,  $\mathbf{Rh^B}$  and  $\mathbf{Rh^C}$ , and to this new factor the symbol  $\mathbf{Rh^D}$  will be assigned and to the corresponding antibody the symbol anti- $\mathbf{Rh^D}$ .

#### TERMINOLOGY

The discovery of blood factors RhA, RhB, RhC and RhD does not necessitate any basic changes in Rh-Hr terminology. They provide further evidence of the special central position of the Rh. factor in the Rh-Hr system. Since "standard" Rh-positive blood has all the factors RhA, RhB, RhC, RhD, etc., this fact need not be indicated in the symbols. Only the rare Rh-positive bloods which lack one or more of the factors RhA, RhB, RhC, or RhD etc., require a special symbol, and in such cases the missing factors are indicated by adding the appropriate superscript small letter. For example, the mother of the erythroblastotic baby in the case of Wiener, Geiger and Gordon has been shown to be of type Rhabrh, while the affected baby is of type Rharh, having inherited the standard Rh<sub>1</sub> agglutinogen from the father, who is of type Rh<sub>1</sub>Rh<sub>1</sub>. The mother became sensitized to the RhA factor but not to the RhB factor, although both of these factors are lacking from her blood cells. while blood factors Rh<sup>c</sup> and Rh<sup>D</sup> are present. In the case of hemolytic transfusion reaction reported by Unger, Wiener and Weiner, 11 the patient's Rh-Hr type proved to be Rhorh, that is, in addition to factor Rh, her blood contained factors Rh, Rh and Rh, but lacked the factor Rh<sup>B</sup>, to which she became sensitized.

#### CASE REPORT

The patient, an eight pound six ounce male newborn Negro infant, was born on February 3, 1959, as the result of his mother's tenth pregnancy. Attention was drawn to him because the direct antiglobulin test on his cord blood was positive, even though both he and his mother were Rh positive.

The mother of the patient gave a history of having received three blood transfusions, the first of one pint of blood in 1948, the second of three pints of blood in 1952, and the third of two pints of blood in 1958. No history of transfusion reactions was elicited, and when the mother's serum was screened on November 26, 1958, no antibodies were found in it. The obstetric history was as follows: The first four pregnancies terminated in 1944, 1947, 1948 and 1951, with the birth at term of normal male infants, all of whom are alive and well. The fifth was also a term pregnancy but the baby, also male, died as a result of an abruptio placentae. The sixth, seventh and eighth pregnancies, in 1954, 1955 and 1957, again yielded normal male babies. The ninth pregnancy, in 1958, terminated by premature rupture of the membranes, and the premature defective baby that was born died after surgery for omphalocele. Thus, there were seven older siblings, all normal boys, alive and well, when the patient, also a boy, was born.\*

\* In this family, of the 10 pregnancies, the sex of nine babies was known to be male. The chance of a family of nine consisting of children all of the same sex is only one in 256. It is worthy of note that some investigators consider a one-in-20 chance sufficient reason to draw such sweeping conclusions as that group O persons are susceptible to duodenal ulcer, or that group A persons are subject to fracture of the femur.

When the positive direct antiglobulin reaction was obtained on the patient's cord blood, further studies were carried out. The hemoglobin concentration proved to be 20.8 gm. per 100 ml., and there was no apparent jaundice, even though the direct antiglobulin test remained positive as late as the third week of life. Since the patient had neither jaundice nor anemia nor any other clinical evidence of disease, no treatment was required. Tests on the mother's serum demonstrated the presence of antibodies paralleling anti-Rho in specificity except that they failed to react with the mother's own red cells. Therefore, further more detailed serologic tests were carried out.

### RESULTS OF SEROLOGIC TESTS

Grouping tests on the mother showed her to be group A<sub>1</sub>, type MN, and type Rh<sub>o</sub>, while the baby was found to be group A, type MN, and type Rh<sub>o</sub>. In the tests with standard Rh-Hr antiserums, the reactions of the bloods of mother and baby were indistinguishable from one an-

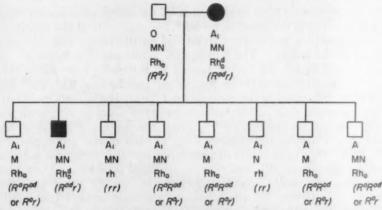


Fig. 1. Family of patient, demonstrating hereditary transmission of agglutinogen  $Rh_{\circ}^{d}$  by the corresponding gene  $R^{cd}$ .

other or from control standard type Rh<sub>o</sub> cells. Yet the mother's serum was found to contain an antibody paralleling anti-Rh<sub>o</sub> in specificity. The serum reacted only weakly by the antiglobulin technic and gave the clearest reactions with ficinated test cells. By that technic, in a 1:4 dilution in preliminary tests, positive reactions were obtained with eight standard Rh<sub>o</sub>-positive bloods and the baby's cells, and negative reactions with 5 Rh<sub>o</sub> variant bloods, three type rh bloods and one type rh" blood. (Later, of course, the series of bloods tested was greatly extended.) In titrations by the ficinated-cell technic, the mother's serum proved to have a titer of 28 units for standard Rh<sub>o</sub>-positive cells, eight units for the baby's cells, and no titer for Rh-negative cells and the mother's own cells. The baby's serum contained antibodies of the same specificity having a titer of 12 units for ficinated Rh-positive cells.

Titration tests were then carried out on the red cells of mother and

October 1959

baby with bivalent and univalent anti- $\mathbf{Rh}_{o}$  serums, as well as univalent antiserums of specificities anti- $\mathbf{Rh}^{A}$ , anti- $\mathbf{Rh}^{B}$  and anti- $\mathbf{Rh}^{C}$ . In these tests the cells of mother and baby gave identical positive reactions and reacted to the same titers as standard  $\mathbf{Rh}_{o}$ -positive cells. Thus, the red cells of both mother and baby contained, in addition to factor  $\mathbf{Rh}_{o}$ , all three factors,  $\mathbf{Rh}^{A}$ ,  $\mathbf{Rh}^{B}$  and  $\mathbf{Rh}^{C}$ . Since the antibody in the serums of mother and baby which clumped  $\mathbf{Rh}_{o}$ -positive cells failed to clump the mother's red cells, which were also  $\mathbf{Rh}_{o}$ -positive, it evidently was defining a blood factor of a new specificity, to which could be assigned the symbol  $\mathbf{Rh}^{D}$ . Therefore, to the antibody itself, the corresponding symbol anti- $\mathbf{Rh}^{D}$  was assigned, and to the Rh agglutinogen in the mother's red cells, the symbol  $\mathbf{Rh}^{d}$ .

### RESULTS OF FAMILY INVESTIGATION

To throw further light on the source of the maternal isosensitization and the heredity of the blood factor RhD, and especially of the agglutinogen Rho, grouping tests were carried out on the father and the other children of the family. The findings are summarized in figure 1. As shown in the figure, the father proved to belong to type Rho. (His blood had, in addition to factor Rho, all the four factors, RhA, RhB, RhC and Rh<sup>D</sup>.) Since two of the children are type rh, the parents must both be heterozygous, that is, the father's genotype must be  $R^{o}r$ , while the mother's genotype must be  $R^{od}r$ . From the mating  $R^{or} \times R^{od}r$ , one would expect among the children 25% of each of the genotypes  $R^{or}$ .  $R^{od}r$ ,  $R^{od}R^{o}$ , rr. Individuals of genotypes  $R^{or}$  and  $R^{od}R^{o}$  are indistinguishable phenotypically, and react as standard type Rho. Thus, from this mating, one would expect 50% type Rh<sub>o</sub>, and 25% each type Rh<sub>o</sub> and type rh children. Actually, among the eight sons in this family, there were five type Rh<sub>o</sub>, one type Rh<sub>o</sub>, and two type rh, which is a satisfactory statistical fit with the genetic theory (Wiener's theory of multiple alleles).

As for the source of the mother's isosensitization, it may be noted that five of the children have the blood factor  $\mathbf{Rh^D}$ , which is lacking from her own red cells. Moreover, the six pints of blood she received by transfusion were all presumably from Rh-positive donors whose blood cells had the  $\mathbf{Rh^D}$  factor. Thus, there was ample opportunity for sensitization to develop, and that antibodies were still not demonstrable in the tests carried out as late as November, 1958, indicates that blood factor  $\mathbf{Rh^D}$  is probably a much weaker antigen than is blood factor  $\mathbf{Rh_0}$ .

#### COMMENT

As has been pointed out, in blood giving standard reactions for blood factor  $\mathbf{Rh_o}$ , blood factors  $\mathbf{Rh^A}$ ,  $\mathbf{Rh^B}$ ,  $\mathbf{Rh^C}$  and  $\mathbf{Rh^D}$  are also present, with only rare exceptions. With blood having an  $\mathbf{Rh_o}$  variant factor ( $\mathbf{\Re h_o}$ -

positive blood), the situation is different. Thus, in tests on  $\mathfrak{R}h_o$ -positive blood specimens for factors  $\mathbf{R}h^A$ ,  $\mathbf{R}h^B$  and  $\mathbf{R}h^C$ , Unger and Wiener<sup>12,13,14,15</sup> found that almost half the specimens lacked one or more of the factors  $\mathbf{R}h^A$ ,  $\mathbf{R}h^B$  and  $\mathbf{R}h^C$ , while when these factors were present they were almost always variants. Preliminary tests suggest that most  $\mathfrak{R}h_o$ -positive bloods lack factor  $\mathbf{R}h^D$ , and that when  $\mathbf{R}h^D$  is present in such blood it is a variant.

With the aid of serums anti- $\mathbf{Rh}^{\mathbf{A}}$ , anti- $\mathbf{Rh}^{\mathbf{B}}$  anti- $\mathbf{Rh}^{\mathbf{C}}$  and anti- $\mathbf{Rh}^{\mathbf{D}}$ , it is now possible to type  $\mathbf{Rh}_{\mathbf{0}}$ -positive cells quickly, and to solve clinical problems where Rh-positive or  $\Re h$ -positive individuals have been sensitized to Rh-positive blood. For example, in a hemolytic transfusion reaction referred to one of us (A. S. W.) for study by Jack and Cahan, the patient's blood type proved to be  $\mathbf{Rh}_{\mathbf{1}}^{\mathrm{cd}}$ rh, that is, while she had standard Rh-positive blood, the cells lacked blood factors  $\mathbf{Rh}^{\mathbf{C}}$  and  $\mathbf{Rh}^{\mathbf{D}}$ . Moreover, two siblings of the patient also proved to have blood of type  $\mathbf{Rh}_{\mathbf{1}}^{\mathrm{cd}}$ rh, and family studies indicate that the agglutinogen  $\mathbf{Rh}_{\mathbf{1}}^{\mathrm{cd}}$  in their red cells is determined by a corresponding allelic gene  $\mathbf{R}^{\mathbf{1}_{\mathrm{cd}}}$ . In another recent case, a patient's blood was referred for study because she was Rh-positive and pregnant and had Rh antibodies in her serum. Typing for blood factors  $\mathbf{Rh}^{\mathbf{A}}$ ,  $\mathbf{Rh}^{\mathbf{B}}$ ,  $\mathbf{Rh}^{\mathbf{C}}$  and  $\mathbf{Rh}^{\mathbf{D}}$  proved her to be type  $\mathbf{Rh}_{\mathbf{1}}^{\mathrm{ab}}$ rh, and the antibody in her serum to be of specificity anti- $\mathbf{Rh}^{\mathbf{A}}$ , as in the original case of Wiener et al.

As Unger and Wiener<sup>13,14,15</sup> have emphasized, in the future, blood factor RhD, as well as factors RhA, RhB and RhC, may well prove to be of greater clinical importance than is factor Rho. The reason for this is that the routine pretransfusion Rh tests permit the identification of Rho-negative individuals so that such patients are not ordinarily transfused with Rh-positive blood. On the other hand, individuals of type Rho, for example, would be classified as Rh positive, and transfusions of Rh-positive blood to such patients could sensitize them to the Rh<sup>D</sup> factor and ultimately give rise to hemolytic transfusion reactions or, as in the present case, to the birth of erythroblastotic babies. Therefore, when enough antiserum becomes available it may be preferable to use anti-RhD (or anti-RhA, or anti-RhB, or anti-RhC) serum for typing prospective recipients of blood transfusions, rather than anti-Rh, serum. In the meantime, it would appear wise that patients with an Rh, variant be given transfusions of Rho-negative blood only, while blood from donors with an Rh, variant factor is used for Rh-positive recipients only.

### SUMMARY

A case is described of subclinical erythroblastosis in the Rh-positive baby of an Rh-positive woman with antibodies in her serum simulating anti-Rh<sub>o</sub> in specificity. The baby was the result of his mother's tenth pregnancy, and the mother had also received three transfusions of a

total of six pints of blood, which could have sensitized her. The anti-body in her serum was shown to be different from anti- $\mathbf{Rh}_{o}$ , anti- $\mathbf{Rh}^{\mathbf{A}}$ , anti- $\mathbf{Rh}^{\mathbf{B}}$  and anti- $\mathbf{Rh}^{\mathbf{C}}$  in specificity, and has therefore been assigned the symbol anti- $\mathbf{Rh}^{\mathbf{D}}$ , with the corresponding blood factor  $\mathbf{Rh}^{\mathbf{D}}$ .

Study of the family showed the mother to be type  $Rh_o^d$  and the father  $Rh_o$ ; since two of the children were type rh, the genotype of the mother had to be  $R^{od}r$  and of the father,  $R^or$ . Of eight children (all sons) in this family, five proved to be type  $Rh_o$ , one type  $Rh_o^d$ , and two type rh, in satisfactory agreement with the expectations according to the genetic theory.

Based on the observations on blood factor  $\mathbf{Rh^D}$ , as well as factors  $\mathbf{Rh^A}$ ,  $\mathbf{Rh^B}$  and  $\mathbf{Rh^C}$ , it is recommended that when patients with an  $\mathbf{Rh_0}$  variant factor require blood transfusion therapy, only Rh-negative donors be used wherever practicable; on the other hand, blood from donors with an  $\mathbf{Rh_0}$  variant factor should be used for Rh-positive recipients only.

#### SUMMARIO IN INTERLINGUA

Un multipara Rh<sub>o</sub>-positive parturiva post su decime pregnantia un infante Rh<sub>o</sub>-positive con leve grados de erythroblastosis fetal. Le anticorpore presente in le sero materne pareva esser de specificitate anti-Rh<sub>o</sub>, sed illo non reageva con le erythrocytos del matre. In le test con cellulas ficinate, le anticorpore monstrava un titro de 28 unitates pro cellulas Rh<sub>o</sub>-positive standard. Illo reageva con le erythrocytos del marito e etiam con le erythrocytos de septe inter le octo infantes vive. In tests preliminari illo non reageva con cinque variantes de sanguine Rh<sub>o</sub>, tres typos de sanguine rh, e un typo de sanguine rh".

Un numero de recente reportos ha describite isosensibilisate subjectos Rhopositive con seros continente anticorpores que pareva esser identic in specificitate con anti-Rho sed que non reageva con le cellulas del subjecto individual mesme e etiam non con le cellulas de altere rar subjectos Rho-positive. Quando le seros ab differente tal casos esseva examinate, il esseva trovate que illos differeva in specificitate non solmente ab anti-Rho sed etiam le unes ab le alteres. Per consequente il pare que in cellulas Rho-positive "standard" il existe altere factores de sanguine associate con le factor de sanguine Rho. Le symbolos RhA, RhB, e RhC habeva jam essite ascribite a tres tal factores. In certe rar subjectos Rho-positive, il pote occurrer que un o plures de iste factores non es representate, e si un tal subjecto deveni isosensibilisate, le resultante anticorporate—anti-RhA, anti-RhB, anti-RhC, etc.—simula anti-Rho in specificitate. In le presente caso le sero differeva in specificitate ab illos previemente describite e pareva indicar le presentia de un nove factor de sanguine associate con Nos ha designate lo como RhD. Viste que sanguine Rho-positive "standard" possede omne le factores de sanguine del serie RhA, RhB RhC, RhD, etc., iste facto non debe esser exprimite per le symbolos. Le rar sanguine Rho-positive in que un o pluros de iste factores es absente pote esser identificate per adder le appropriate minusculo in position elevate. In le presente caso le agglutinogeno in le érythrocytos del matre es identificate como Rho.

Un studio del familia in le presente caso es summarisate in figura 1. Proque duo del infantes es del typo rh, le parentes debe esser heterozygotic. Le genotypo del patre debe esser  $R^{or}$  e illo del matre  $R^{od}r$ . Ex le union de  $R^{or}$  con  $R^{od}r$ , on expecta un prole con 25% de cata un del genotypos  $R^{or}$ ,  $R^{od}r$ ,  $R^{od}R^{o}$ , e rr. Individuos del genotypos  $R^{or}$  e  $R^{od}R^{o}$  non pote esser distinguite phenotypicamente. Illes reage

como Rho standard. Assi, in le caso del presente union on expectarea un prole con 50% del typo Rho, 25% del typo Rhd, e 25% del typo rh. In realitate, le octo filios in iste familia includeva cinque del typo Rho, un del typo Rhd, e duo del typo rh. Statisticamente isto es un correlation satisfacente con le theoria genetic (le theoria del alleles multiple de Wiener). Tests preliminari suggere que le majoritate del sanguines  $\mathfrak{G}$ ho-positive es sin le factor RhD e que, quando isto es presente, il se tracta etiam de un variante.

Con le adjuta de seros anti- $\mathbf{Rh^A}$ , anti- $\mathbf{Rh^B}$ , anti- $\mathbf{Rh^C}$ , e anti- $\mathbf{Rh^D}$ , il es possibile resolver problemas clinic in que subjectos Rh-positive o  $\mathfrak{Rh}$ -positive ha essite sensibilisate a sanguine Rh-positive. Quando un sufficiente numero de tal seros deveni disponibile, illos va sin dubita esser plus utile in le typation de candidatos pro le reception de sanguine que sero anti- $\mathbf{Rh_0}$ . Intertanto il pare recommendabile que patientes con sanguines variante de  $\mathfrak{Rh_0}$  recipe transfusiones exclusivemente de sanguine  $\mathbf{Rh_0}$ -negative e que sanguine ab donatores con typo variante de  $\mathfrak{Rh_0}$  es usate solmente pro recipientes Rh-positive.

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# RECENT DEVELOPMENTS IN THE LABORATORY DIAGNOSIS OF SYPHILIS\*

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From 1947 to 1955, one of the most unusual and precipitous declines in the reported morbidity of a chronic, social, communicable disease ever observed in the history of our country was recorded. This disease was syphilis. As can be noted in table 1, there was roughly a 68% decline in reported cases of syphilis during these years. The rates for this disease declined over 71%, while cases of infectious syphilis declined approximately 94% during the same time. Observe further that since 1955 there appears to be a leveling off or plateau of reported cases. This leveling off of total syphilis can tend to mislead us in estimating the future unless we are aware that the rates of infectious syphilis have been rising slowly, consistently and

ominously from 1955 to the present.

The bulk of undiscovered syphilis in the past, today and for the foreseeable future is latent syphilis. This stage of syphilis, so aptly named latent or "hidden," presents no signs, symptoms or findings in the patient other than those demonstrated by appropriate serologic testing. Until the last decade, the various serodiagnostic tests for syphilis measured the presence of Wassermann antibody or reagin in the patient's serum. Since the work of Landsteiner in 1907,1 it has been known that reagin is not a specific antibody for syphilis, and may appear during the course of many other diseases, vaccinations, drug treatment and the like. In spite of the lack of specificity of reagin, it was demonstrated and empirically accepted that the sensitivity of reagin tests could be adjusted so that most people with syphilis would react to the test, while most people not having syphilis would not react. Prior to the advent of penicillin, when syphilis was plentiful, this system worked admirably—so much so, in fact, that most people considered that the diagnosis of syphilis with the help of the laboratory was a relatively simple procedure, whereas proper treatment of the disease was considered to be more difficult, requiring special knowledge. This situation has now reversed itself. Treatment of this disease has been simplified to the point

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where any competent physician can do an excellent job, while diagnosis has become more difficult, in view of the rapid decline of the disease, a presumed increase in the incidence of diseases associated with biologic false-positive (BFP) reagin reactions, and a multitude of new serodiagnostic tests for syphilis.

Several workers have observed that the general incidence of reagin reactivity of presumed "normal" populations is 1:4,000, or, expressed as a rate, 25 per 100,000 population.<sup>2, 3</sup> As the amount of syphilis decreases in the population and the number of reagin reactors not related to syphilis remains relatively constant, the usefulness of the reagin test as a diagnostic procedure in syphilis diminishes until finally more people react to reagin

TABLE 1

Cases and Rates of Syphilis Reported for Continental U. S.
Fiscal Year 1947–1958

Year	Cases	Rates per 100,000
1947	372,963	264.6
1948	338,141	234.7
1949	288,736	197.3
1950	229,723	154.2
1951	198,640	131.8
1952	168,734	110.8
1953	156,099	100.8
1954	137,876	87.5
1955	122,075	76.0
1956	126,219	77.1
1957	135,542	81.2
1958	126,072	74.0

tests who do not have syphilis than do those who have the disease. As an example, compare the rate of 25 per 100,000 population reacting to such tests but not having syphilis, to the reported rate of syphilis in the State of South Dakota in 1957, which was 24 per 100,000 population. If we assume both figures to be a valid expression of reagin reactivity, it would be less expensive and much more time-saving for the physician in South Dakota merely to flip a coin to decide whether his patient with a positive Kahn test had syphilis or a BFP. Among some population groups in this country there are more BFP reactors than there are those reacting because of syphilis. Under such circumstances, the clinician faces the frustrating problem of having to attempt to determine whether a reactive standard serologic test for syphilis represents that disease or some other condition, possibly one with an even poorer prognosis than syphilis.

During the last decade, laboratory researchers, being aware of the previously discussed trends, have directed their attention to developing more specific tests for syphilis. The direction of this work initially was a return to studying *Treponema pallidum*, the etiologic agent of this disease, in an attempt to develop a more specific antigen for serodiagnostic testing. Such antigens reacting specifically with antibodies developed in the host during

TABLE 2

### Treponemal Tests for Syphilis

1949	TPI	Treponema pallidum Immobilization tests	
1953-55	TPA	Treponema pallidum Agglutination tests	
1953	TPIA	Treponema pallidum Immune-Adherence tests	
1955	TPCF	Treponema pallidum Complement Fixation test	
1956	TPMB	Treponema pallidum Methylene Blue tests	
1956	WTPCF	Whole-body Treponema pallidum Complement Fixation test	
1957	RPCF	Reiter Protein Complement Fixation tests	
1957	TWR	Treponemal Wassermann Reaction test	,
1957	FTA	Fluorescent Treponemal Antibody test	
1958	TPCP	Treponema pallidum Cryolysis Protein tests	

the course of infection with syphilis would tend to solve the growing problem of BFP reactions to the standard reagin tests.

Table 2 represents the chronologic development of the newer treponemal serologic tests for syphilis. Note that these tests are designated by descriptive terms rather than by the names of the authors who developed them. This was done in an attempt to indicate, in general, the type of test and antigen employed. Unfortunately, the common practice of designating these tests by letters somewhat defeats the purpose of identification of the test. If one considers the letter designation alone, there is a confusing "alphabet soup" for consideration. This letter abbreviation method, plus the clinician's lack of knowledge of these tests, leaves him in a precarious position in deciding what test to employ for his particular patient and how to interpret the test result obtained.

Table 3 classifies these tests by certain characteristics of the antigen used in the test procedures. Such a classification would appear to make this group of tests less confusing to the clinician, and one from which he can

#### TABLE 3

### Current Treponemal Tests for Syphilis

- I. Those tests using whole-body virulent Treponema pallidum (Nichols strain) as antigen
  - A. Those using viable organisms

    - Treponema pallidum Immobilization (1949)
       Treponema pallidum Methylene Blue (1956)
    - Those using, or usually using, nonviable organisms

      - Treponema pallidum Agglutination (1953–55)
        Treponema pallidum Immune Adherence (1953)
        Whole-body Treponema pallidum Complement
        Fixation (1956)
      - (3)
  - (4) Fluorescent Treponemal Antibody (1957)
- II. Those tests using a chemical fraction derived from whole-bodyvirulent Treponema pallidum (Nichols strain) as antigen
  - Treponema pallidum Complement Fixation (1955) Treponemal Wassermann Reaction (1957)

  - Treponema pallidum Cryolysis Protein (1958)
- Those tests using a chemical fraction derived from whole-body Reiter treponeme as antigen
  - Reiter Protein Complement Fixation (1957)
  - Kolmer Test with Reiter Protein Antigen (1958)

deduce certain useful information. For instance, the separation of the whole-body antigen treponemal tests into those using viable organisms as opposed to those utilizing the nonviable organisms immediately tells the physician that he must guard against the presence of penicillin or any other antitreponemal agent in the serum presented for testing. In such tests, antibiotics in the serum may kill the living organisms and produce an inconclusive result. Under such circumstances, the physician should not consider the utilization of such test procedures or, if he requires them, he must inform the laboratory concerning treatment history so that the antitreponemal agent can be inactivated if possible prior to running the test.

Although the current treponemal tests for syphilis here discussed represent only 10 of 20 such tests being performed (in various stages of development) in 28 major laboratories throughout the world, those we will consider are the major tests of this group, and are representative of the different approaches investigators have taken to develop more specific tests for syphilis. As descriptive review articles concerning most of the treponemal tests are available, as well as the original and subsequent publications, I will not take the time to go into technical details in the performance of the

tests.

The Treponema Pallidum Immobilization (TPI) test 5 ushered in the era of treponemal tests for syphilis in 1949. This difficult, time-consuming, highly technical and expensive procedure is an excellent test for syphilis in spite of its lack of sensitivity and failure to identify early syphilis until long after all other procedures are positive. In the TPI test, living organisms are counted by dark field microscopy after having been submitted to the patient's serum and complement. The proportion of motile versus immobilized organisms determines whether the test is positive. If the majority of the organisms are not motile the test is positive; if they remain motile, the test is negative. The cost of this test in private laboratories varies between 30 and 100 dollars. The Treponema Pallidum Methylene Blue (TPMB) test 6 is very similar to the TPI test, with the exception that when the slide is prepared for counting of the treponemes, methylene blue is added. In the presence of antibody, uptake of the dye by the organism is inhibited. An unstained organism, therefore, is presumed to be immobilized. Hence, if the organisms are not stained, the test is positive. Staining is interpreted as negative. This test is not available currently to the private physician.

The Treponema Pallidum Agglutination (TPA) tests <sup>7,8</sup> employ intact killed treponemes. Such test procedures have the general disadvantages of any agglutination procedure, which is the relative difficulty in determining the status of the weakly reactive specimen. Again, neither of these pro-

cedures is generally available to the practitioner.

The Treponema Pallidum Immune Adherence (TPIA) test 9, 10 allows for the adherence of treponemes to red blood cells in the presence of com-

plement which, when followed by gentle centrifugation, sediments the red cells and causes a disappearance of the treponemes from the supernatant fluid when the test is positive. Antigen for this test procedure is produced by one commercial firm, and hence is potentially available to the physician; however, this relatively useful procedure has seen little application to date in this country.

The Whole-body Treponema Pallidum Complement Fixation (WTPCF) test <sup>11</sup> employs the TPIA antigen in the Kolmer type of complement fixation procedure. While this is an interesting application of this antigen, lack of extensive evaluation of the procedure in relation to syphilis precludes its

recommendation at present.

The Fluorescent Treponemal Antibody (FTA) test <sup>12</sup> is accomplished with a dried drop of treponemal suspension on a slide to which is added a drop of human serum. After permitting the reaction to take place, the slide is washed and fluorescein-tagged human antiglobulin is added. If the unknown serum contains antibody, such will be adsorbed on the treponeme and will then combine with the tagged antiglobulin. Fluorescence of the tagged organism is detected by use of the ultraviolet microscope. This is an excellent test procedure that can be accomplished within a half-hour; however, the current cost of the ultraviolet microscope and lack of availability of standardized commercial antigen do not allow for wide availability of this very excellent test at present. It has been hypothesized that the antibody measured in this procedure may be similar or identical to that measured by the TPI test. <sup>18</sup>

All of the above described tests have one or more of the following disadvantages: lack of test reproducibility, lack of antigen standardization, lack of commercially available antigen, high cost, and technical difficulty

of performance.

While the three tests listed under II in table 3 represent a tremendous stride in the direction of overcoming the abovementioned difficulties, encountered with tests listed under I, in table 3, they nevertheless all have one common difficulty. This difficulty arises from the necessity of utilizing Treponema pallidum as antigen. Inability to culture the organism in the laboratory necessitates animal inoculation and recovery, which in itself is an expensive procedure.

The Treponema Pallidum Complement Fixation (TPCF) test <sup>14,15</sup> represents the second high-water mark in the era of treponemal tests. Historically, this is the first successful and practical test devised utilizing a chemical fraction derived from the etiologic agent of syphilis. Antigen is available commercially from three sources in this country. This protein-aceous extract is employed in a conventional complement fixation test. An improved version of this procedure, known as the "tpcf 50" test, <sup>16</sup> permits accomplishment of the test in a few hours instead of overnight, with an apparent increased specificity and reduction in cost of the procedure.

For the original TPCF procedure, the antigen costs approximately 3 dollars per test dose, whereas with the "tpcf 50" procedure the cost is reduced to

approximately 35 cents per test dose.

The Treponemal Wassermann Reaction (TWR) test, <sup>17, 18</sup> introduced by Price in England, obtains its fraction by mechanical disruption of *T. pallidum* and employs it in a complement fixation procedure. While the test may show promise, lack of evaluation of the procedure abroad and in this country, and the lack of a commercially available source of antigen, limit

the usefulness of this procedure to the physician at present.

The Treponema Pallidum Cryolysis Protein (TPCP) tests, 19, 20, 21 while again not available to the physician, represent very excellent procedures that are offered here as historic landmarks in the development of better, more reproducible and less expensive treponemal tests for syphilis. The test as developed in this country and reproduced shortly thereafter in Italy utilizes a protein fraction of T. pallidum obtained by cycles of freezing and thawing according to the technic of D'Alessandro and Dardanoni,22 which is identical with the technic utilized in the production of Reiter protein antigen. While using this antigen production technic on both the etiologic agent of syphilis and the Reiter organism, we were able to demonstrate that the chemical obtained from both the pathogenic and the nonpathogenic treponeme was immunologically and serologically identical. Hence one can utilize the material obtained from the Reiter organism in the serodiagnosis of syphilis with confidence, as it represents an antigen present in Treponema pallidum to which the human host reacts by producing antibodies during the course of the disease.

As the Reiter organism, which is the source of antigen for the tests listed under III, in table 3, may be grown in large quantities quite inexpensively by culture technics in the laboratory, the cost of producing such an antigen is greatly reduced over the II-type tests. The Reiter Protein Complement Fixation (RPCF)<sup>28</sup> and the Kolmer test with Reiter Protein Antigen (KRP)<sup>24</sup> tests are practically identical in that they utilize a chemical fraction derived as described above in a Kolmer complement fixation procedure. Antigens for these tests are fairly well standardized and available from four commercial distributors in this country. The cost for these procedures is approximately 2 cents per test dose of antigen.

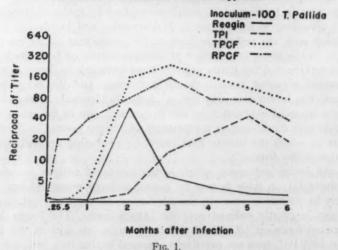
Hence, in less than a decade, the research laboratories have developed procedures for very effective treponemal serodiagnosis at low cost and

available to all who would wish to use them.

Some physicians have been led to believe that, although reagin or Wassermann tests are not specific for syphilis, the newer treponemal tests, such as those here described, are specific for syphilis. In other words, a TPI-positive means syphilis, and a TPI-negative means a patient does not have syphilis. This is an unfortunate fallacy, in that it attributes infallibility to the results of a laboratory procedure. No serologic test for syphilis diag-

noses syphilis; rather, its result informs us of the immunologic status of the patient in relation to the antibody being tested. None of these antibodies measured is absolutely specific for syphilis alone. In fact, practically all of the related treponemal diseases in man react to these test procedures; in addition, certain antigenic components isolated from nonpathogenic treponemes will react with syphilitic antibodies. 19, 20, 21 Luckily for us in this country, at least, there are few treponematoses other than syphilis, and hence we can place a practical reliance upon the results of some of the treponemal tests as being related to syphilis in our patients. It should be strongly noted that reagin, TPI, TPCF and RPCF test antibodies are all different immunologic host responses. There is variability in the appear-

### Development of Reagin, TPI, TPGF and RPCF Antibodies in Untreated Rabbit Syphilis



ance of these antibodies in time after infection, and in their course during the natural history of syphilis. This variation is to be noted in figure 1. Under the conditions of the experiment from which these data were obtained, I call your attention to the fact that, if test specimens were taken just prior to the first month after infection, the results of that testing would be: TPI—negative; reagin—weakly reactive; TPCF—positive, but of relatively low titer; and RPCF—positive at a relatively high titer. If this were a patient and the physician had a blind reliance in the TPI test, he would be likely to conclude that the low titer reagin test in the fact of a negative TPI represented a biologic false-positive, when in fact the patient would be infected with syphilis.

It is essential that the physician be aware of the above to interpret ade-

quately such test results from his patient. To add to the confusion, we now know that treatment, adequate and probably inadequate, changes the pattern of at least some of these antibodies. Current research is only now beginning to clarify the meaning of these changes during and after adequate and inadequate treatment. Without a grasp of the significance of these facts, the physician simply cannot correctly interpret the apparent contradictory and confusing findings among nontreponemal and treponemal tests in his patient. Further, without such knowledge the physician is less likely to use the proper test at the proper time, as such information is mandatory to exploit

the special limitations and usefulness of these test procedures.

To be a bit more practical, even though both false-positive and false-negative test results have been observed for all the treponemal tests, such observations represent such a small number of cases when compared with reagin results that the special usefulness of almost all of the treponemal tests is in the differentiation of the chronic biologic false-positive reactor and the patient with syphilis. All of these new procedures may seem to some to complicate rather than to simplify the serodiagnosis of syphilis. The opposite is true if the physician acquires sufficient knowledge properly to evaluate the test results in relation to the status of his patient. It is essential, then, that the physician divest himself of the fallacy that the laboratory result can substitute for his brains and knowledge. For the full exploitation of the research advances in this field, there is simply no substitute for a physician well informed about syphilis as a disease, well informed about his patient, and well informed about the implication of the test results he receives from the laboratory.

In closing, I would like to comment briefly upon an innovation in testing of reagin antibody which our labora bry has made available, namely, the Rapid Plasma Reagin (RPR) test.<sup>25</sup> Previously, attempts to obtain a satisfactory test procedure for the utilization of unheated serum or plasma met with failure; however, we have been able to overcome this difficulty, and to decrease time, personnel and technical equipment necessary to test for this antibody. The test can be accomplished with a minimum of equipment (which may be throw-away materials if desired), with test results available within 10 minutes from the time the blood specimen is drawn from the patient. The RPR test is slightly more sensitive than standard reagin procedures, such as the VDRL slide test; however, it loses little or none of its specificity as a reagin procedure.<sup>26</sup> Currently, it is the routine test employed on all migrant agricultural workers passing the Mexican-American border, and, among other places, is currently being utilized in Chicago for the screening of jail population groups.

In conclusion, there have been five major developments in the serology of syphilis in the last 10 years: the TPI test, the TPCF test and modifications, the RPCF test, the Rapid Plasma Reagin test and the Fluorescent Treponemal Antibody test.

Although the full impact of these procedures has not yet been felt, it may be anticipated that they will play an ever-increasing role in the diagnosis, treatment follow-up and control of syphilis and related treponemal diseases. The cost factors in relation to the application of these test procedures are such that it may be further anticipated that the routine serology of syphilis will consist of an inexpensive, rapid screening procedure such as the RPR test adapted to serum, followed by a Reiter antigen test on all reagin reactors. While the use of other treponemal procedures may be required and used in special instances, the bulk of these procedures remains unavailable, or too expensive for either the taxpayer or the patient, in view of the advent of these other available, reliable, time-saving and inexpensive serodiagnostic technics.

#### SUMMARIO IN INTERLINGUA

Le precipitose declino de syphilis in le Statos Unite inter 1947 e 1955, quando le nonspecific tests serologic anticorporee de Wassermann esseva ancora in uso, ha reducite le utilitate de tal technicas diagnostic in vista del relativemente constante quotiente de reactivitate biologic falsemente positive in le population.

Le reportate morbiditate de syphilis descendeva per 68 pro cento in le curso de ille periodo, durante que le incidentia descendeva per 71 pro cento e le frequentia de precoce syphilis infectiose per 94 pro cento. Depost 1955 un certe horizontalisation del curvas de frequentia e de incidentia ha essite notate, e precoce syphilis infectiose ha manifestate un lente sed uniforme augmento.

Le observation de iste tendentias ha stimulate in le curso del passate decennio recercas laboratorial resultante in le disveloppamento de tests serologic treponemal e nontreponemal pro le detection de syphilis.

Dece ex 20 nove tests treponemal, in uso in 28 major laboratorios de recerca in varie partes del mundo, es identificate e describite in terminos general. Illos es (1) tests de Immobilisation de Treponema Pallidum (ITP), (2) tests de Agglutination de Treponema Pallidum (ATP), (3) tests de Adherentia Immun de Treponema Pallidum (AITP), (4) tests de Fixation de Complemento de Treponema Pallidum (FCTP), (5) le test de Treponema Pallidum a Blau Methylenic (TPBM), (6) le test de Fixation de Complemento de Treponema Pallidum a Corpore Total (FCTPC), (7) tests de Fixation de Complemento a Proteina de Reiter (FCPR), (8) le test del Reaction Wassermann Treponemal (RWT), (9) le test de Anticorpore Treponemal a Fluorescentia (ATF), e (10) le tests de Cryolyse de Proteina de Treponema Pallidum (CPTP).

Le test FCPR—viste que illo ha essite ben evalutate, que illo es facile a effectuar, que le antigeno usate in illo es commercialmente disponibile, e que iste antigeno es incostose (2¢ per dose)—pare esser al tempore presente le plus utile pro le medico practicante.

Le characteristicas del disveloppamento del differente, relativemente specific anticorpores treponemal durante le curso natural del infection e le dependentia del tractamento (si on vole render lo adequate) del titro de iste differente systemas de anticorpore explica le necessitate pro le medico de comprender tal factores si ille desira usar e interpretar efficacemente le resultatos del mentionate nove technicas serodiagnostic.

Ben que nulle test treponemal es absolutemente specific pro syphilis e ben que reactiones falsemente positive e falsemente negative ha essite observate in omne le varie tests, lor grado de specificitate practic in le Statos Unite in comparation con

illo del tests a reagina rende los utile in le differentiation del patiente con syphilis ab le subjecto con reaction biologic falsemente positive.

Pro le rapide e incostose identification de anticorpore de Wassermann o reagina, le test a Reagina Plasmatic Rapide (RPR) ha essite disveloppate e modificate de maniera que illo pote esser executate con plasma o noncalefacite sero. Iste test require un minimo de apparatura e de personal, e le resultato es cognoscite intra 10 minutas post le tempore quando le specimen de sanguine es prendite ab le patiente. Le test RPR es levemente plus sensibile que methodos standard a reagina (como le test VDRL a lamina). Tamen, illo perde pauco o nihil de su specificitate como technica a reagina. Currentemente illo es le test de routine usate pro omne migrante obreros agricultural qui transversa le frontiera inter Mexico e le Statos Unite. Illo es etiam usate in plure grande citates pro le investigation de populationes de prison.

Le passate decennio ha vidite quatro major disveloppamentos in le serologia de syphilis: (1) Le test ITP, (2) le test FCTP e su modificationes, (3) le test FCPR,

e (4) le test RPR.

Ben que le impacto total de iste technicas es non ancora apparente, illos va haber un semper crescente function in le diagnose, le observation post-tractamental, e le suppression de syphilis e de morbos treponemal affin. Le situation del costos resultante del application de iste methodos es tal que on pote predicer que le serologia routinari pro syphilis va consister de un rapide e incostose technica de scrutinio in massa, como le test RPR, sequite per un test antigenic de Reiter in le caso de omne reactiones positive a reagina. Ben que le uso de altere technicas treponemal va possibilemente remaner inevitabile in casos special, le majoritate de iste altere technicas non es disponibile o remane troppo costose pro le patiente si ben que como pro le stato.

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# RENAL FAILURE IN LAENNEC'S CIRRHOSIS OF THE LIVER. I. DESCRIPTION OF CLINICAL AND LABORATORY FEATURES \*

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In 1863 Austin Flint first called attention to the presence of oliguria in patients with cirrhosis of the liver and hydroperitoneum. Since that time it has become quite apparent that oliguria is extremely common in patients with cirrhosis and marked ascites. This decreased urine flow is generally not associated with striking diminution in glomerular filtration rate (GFR) or rise in blood nonprotein nitrogen concentration; 2 rather, the oliguria is usually attributable to the decreased solute load, especially sodium, that is presented for excretion. However, in some instances, decreased urine flow in patients with cirrhosis is accompanied by azotemia. While we have referred to certain aspects of a limited number of these patients with renal failure in a previous article,2 it is the purpose of the present report to describe the group of 22 patients in more detail, and to consider the possible pathogenesis of this syndrome.

Renal failure in the course of cirrhosis of the alcoholic is one of the conditions that have been included in the broad term, "hepatorenal syndrome." This designation will not be used in the present report, since it would serve no particular purpose to do so, and since so much confusion has developed concerning its meaning.

#### OBSERVATIONS

For convenience, we have divided our series of 22 patients into four somewhat arbitrary groups, according to the special circumstances prevailing at the time of renal failure. We shall describe individual "representative" cases from each group in some detail, and then summarize some of the special features presented by other cases whose renal failure developed under similar circumstances.

Group I-Mild gastrointestinal bleeding-nine patients. Patients with hemorrhage sufficient to produce a significant reduction in hematocrit or clinical evidence of shock were excluded from the series.

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#### CASE REPORTS

Case 1 (table 1). A 48 year old alcoholic male bartender had been in good health until four months before admission, when he thought his urine had become darker in color. He had also noted jaundice for the preceding 10 days, and ascites for three to four days. On physical examination he appeared to be acutely ill, and was deeply jaundiced. He had a markedly protuberant abdomen, although it was not tense with fluid. He also had spider nevi and palmar erythema. On admission his blood pressure was 130/70 mm. Hg; serum bilirubin, 24 mg./100 ml.; stool guaiac test, negative; hematocrit, 36%. Serum sodium concentration was 132 mEq./L.; blood nonprotein nitrogen, 25 mg./100 ml.; urine specific gravity, 1.025, with 1 plus albumin, and occasional white cells and red blood cells. The next day his urine had a specific gravity of 1.022, with a trace of albumin. During the second week of hospitalization the patient became increasingly jaundiced and generally appeared to be more seriously ill. At the same time, urine volume decreased from 700 ml./day at the beginning of the week to 300 ml./day at the end of the week. In that same period his blood pressure appeared to be somewhat lower, and his stools contained some blood, although his hematocrit remained unchanged. Serum sodium concentration declined, nonprotein nitrogen rose sharply, and the concentration of his scanty urine was only 375 milliosmolal (specific gravity 1.010). Within the next few days, urine flow decreased to less than 50 ml./day, without further concentration; blood pressure decreased a bit more, serum bilirubin concentration remained unchanged; the stools continued to contain occult blood without change in hematocrit or evidence of shock; serum sodium concentration was close to its initial value, and the nonprotein nitrogen rose to 188 mg./100 ml., with serum creatinine of 14.3 mg./100 ml. On the nineteenth hospital day the patient became comatose and died.

In summary, this patient with symptomatic liver disease of short duration entered the hospital with normal blood nonprotein nitrogen and a concentrated urine. Within a period of approximately two weeks he had impairment in the ability to concentrate the urine, became virtually anuric, with the highest blood nonprotein nitrogen and serum creatinine concentrations in our series, and died. This episode was associated with gastrointestinal bleeding of a mild degree, a fall in blood pressure, increased jaundice, and little change in serum sodium concentration.

Figure 1 shows the kidney structure to be essentially normal except for some dilatation of the tubules.

# Remaining eight patients in Group I:

Clinical and laboratory features:

- 1. Age: 38-68.
- 2. Duration of symptomatic liver disease: one week to two years.

TABLE 1
Case 1

	10/8	10/15-21	10/22-26
Blood pressure (mm. Hg) Bilirubin (mg./100 ml.) Stool guaiac Hematocrit (per cent) Serum sodium (mEq./L.) NPN (mg./100 ml.) Urine volume (ml./24h.) Urine concentration	130/70 24 0 36 132 25 1.025	110/60 . 34 2+ 35 125 68 700-300 1.010 (375 mOsm./L.)	90/50 32 3+ 35 129 188 <50 1.011 (380 mOsm./L

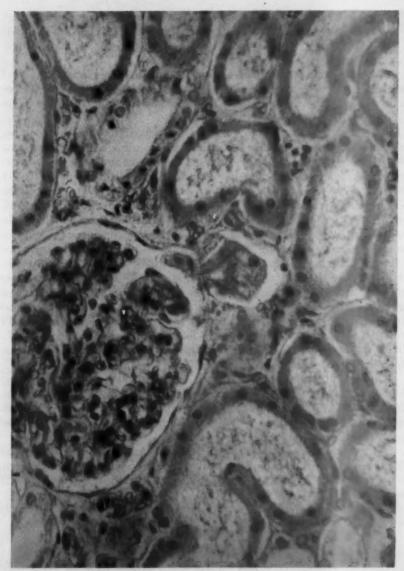


Fig. 1. Case 1. Microscopic appearance of the kidney.

- 3. Ascites: marked in six, moderate in one, minimal in one.
- 4. Peripheral edema: minimal to marked in six, absent in two.
- 5. Initial serum bilirubin concentration: 2.0 to 16 mg./100 ml. In three patients, renal failure developed while jaundice increased; in

three instances, while serum bilirubin concentration was decreasing; and in two patients, while the serum bilirubin remained unchanged.

Urine: acid; frequently but not always contained albumin, hyaline and granular casts, and red blood cells.

Course of renal failure: In several patients there was evidence of normal renal function, as determined by serum creatinine concentration,\* endogenous creatinine clearance (inulin and para-aminohippurate (PAH) clearance in three patients), urinary concentration and phenolsulfonphthalein (PSP) excretion, two to four months before their deaths. In addition, in six of the eight patients the blood nonprotein nitrogen (or serum creatinine concentration) was normal and the urine concentrated (specific gravity greater than 1.020, or solute concentration greater than 600 milliosmolal) three to seven weeks before death in renal failure. In two instances the serum creatinine concentration rose while the urine remained concentrated, and within a few days, while still oliguric, the urine became more dilute. In two instances a significant rise in serum creatinine concentration and impaired concentrating ability were documented to occur within a period of 24 hours. Serum sodium concentration varied from 116 to 130 mEq./L. shortly before death. In four patients, serum sodium concentration was no lower than when renal function was known to be normal, and in one patient, renal failure developed while the serum sodium concentration was 143 mEg./L. Serum bicarbonate concentration varied from 12 to 19 mMol./L., except in case 1, reported above, when it decreased to 8 mMol./L. In all instances, blood pressure decreased to a degree comparable to that described in case 1.

One patient, with normal clearances of inulin and PAH one month before death, demonstrated a steadily rising blood nonprotein nitrogen (from 26 to 118 mg./100 ml.) over a two-week period despite the fact that his urine volume varied from 900 to 1,000 ml. daily. The urine remained poorly concentrated throughout.

Once renal failure was observed, it was found to be progressive, and death occurred within from five to 30 days. Maximal blood nonprotein nitrogen shortly before death varied from as low as 55 mg./100 ml. to 118 mg./100 ml.

Postmortem examination, performed in six patients, revealed essentially normal kidneys except for bile staining in those with marked jaundice.

# Group II-Following abdominal paracentesis-three patients,

Case 2 (table 2). A 42 year old unemployed alcoholic male had had jaundice and ascites intermittently for less than a year before death. He was admitted in June, 1957, because of increasing ascites and abdominal discomfort. On physical

<sup>\*</sup>Normal range of serum creatinine concentration in this laboratory is 0.6 to 1.3 mg./100 ml. Patients with decompensated cirrhosis frequently have low serum creatinine concentrations, presumably due to muscle wasting. Consequently, a serum creatinine of 1.0 mg./100 ml., ordinarily within the normal range, might well represent a significant reduction in endogenous creatinine clearance and glomerular filtration rate.

examination he had mild jaundice and tense ascites. In March, 1957, four months before death, the patient was hospitalized and was found to have marked ascites, some jaundice, a blood pressure of 120/70 mm. Hg, serum sodium concentration of 125 mEq./L., nonprotein nitrogen of 25 mg./100 ml., and creatinine clearance of 145 ml./min. Urine concentrated to 1.025, with a trace of albumin. At the time of his readmission, in June, 1957, he had findings quite similar to those listed in March, 1957. Paracentesis was performed at the beginning of July because of persistent abdominal pain. Within one week he was noted to be lethargic and oliguric with a nonprotein nitrogen of 68 mg./100 ml. The last column of table 2 lists some of the data obtained just before death two weeks after paracentesis. At that time his serum bilirubin concentration was the same as on admission, his blood pressure was reduced, serum sodium concentration was lower, his nonprotein nitrogen was 90 mg./100 ml., but he was still able to elaborate a concentrated urine. He never had evidence of gastrointestinal bleeding.

### TABLE 2 Case 2

	March and June, 1957	July, 1957
Blood pressure (mm. Hg)	120/70	100/60
Bilirubin (mg./100 ml.)	3-4	3.2
Stool guaiac	0	0
Hematocrit (per cent)	38	38
Serum sodium (mEq./L.)	125	. 117
NPN (mg./100 ml.)	25	90
Creatinine clearance (ml./min.)	145	20
Urine volume (ml./24h.)	?	< 50
Urine concentration	1.025	1.025
		(800 mOsm./L.)

In summary, this patient developed renal failure shortly after paracentesis, without evident bleeding and in the absence of marked or progressive jaundice. Urinary concentration was sustained. Figure 2 demonstrates an essentially normal renal structure.

# Remaining two patients in Group II:

Clinical and laboratory features:

- 1. Age: 40, 62.
- Duration of symptomatic liver disease: less than one year, more than two years.
- 3. Ascites: tense.
- 4. Peripheral edema: minimal, moderate.
- 5. Initial serum bilirubin concentration: 2.6, 17 mg./100 ml. No significant change during renal failure.
- 6. Urine: acid, trace of albumin and occasional red blood cells.

Course of renal failure: One patient had a nonprotein nitrogen of 24 mg./100 ml., serum creatinine of 0.5 mg./100 ml., an endogenous creatinine clearance of 120 ml./min., and a phenolsulfonphthalein excretion of 65% in two hours; random urine concentrated to 1.016 only three weeks before the paracentesis which was performed to relieve abdominal discomfort. Only 5,000 ml. of fluid were removed. Within a few days the pa-

tient was observed to be anuric, with a decrease in blood pressure from 116/70 to 105/60 mm. Hg, and a serum bicarbonate concentration of 12 mMol./L. He remained anuric for the last 10 days of life, reaching a maximal serum creatinine concentration of 5.2 mg./100 ml. before death in hepatic coma.

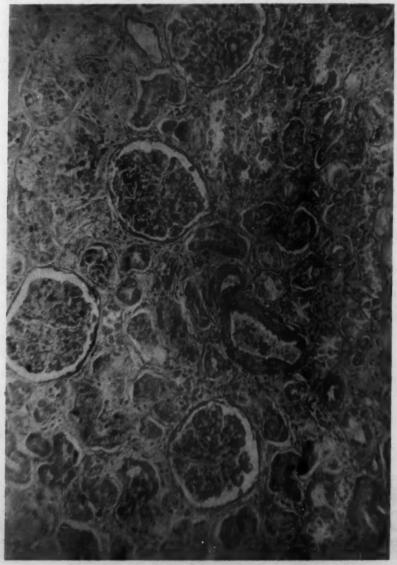


Fig. 2. Case 2. Microscopic appearance of the kidney.

The other patient was observed to have a nonprotein nitrogen of 25 mg./100 ml. and a urine specific gravity of 1.020 the day before abdominal paracentesis was performed for discomfort. Within one week after the fluid was removed, his blood nonprotein nitrogen was 55 mg./100 ml. and he was oliguric, with a urine specific gravity of 1.014. Within another week he died in hepatic coma, with a blood nonprotein nitrogen of 108 mg./100 ml. His last urine specific gravity was 1.009. Blood pressure was observed to decrease after paracentesis.

Both patients had reduced serum sodium concentration. One patient's serum sodium concentration was no lower than when he had normal renal function.

# Group III—Severe or progressive jaundice—five patients.

Case 3. A 50 year old male manual laborer, a chronic alcoholic, was admitted to the hospital complaining of swelling of the abdomen and jaundice of five days' duration. Two years previously he had been hospitalized for impending delirium tremens, at which time there was no evidence of liver disease, and his urine specific gravity was 1.027. Physical examination on this final admission revealed a man who appeared to be acutely ill, with a blood pressure of 130/80 mm. Hg, many spider nevi, severe jaundice, marked ascites without peripheral edema, and a large, tender liver. Urine specific gravity was 1.020, with a trace of albumin. Blood nonprotein nitrogen was 20 mg./100 ml.; serum sodium, 125 mEq./L.; serum albumin, 3.0 gm./100 ml.; serum bilirubin, 23 mg./100 ml. On the following day, urine specific gravity was again 1.020, with a nonprotein nitrogen of 25 mg./100 ml. On the third day of hospitalization the patient became confused, developed a "liver flap," and was more deeply jaundiced (serum bilirubin, 30 mg./100 ml.). On that day the blood nonprotein nitrogen was 46 mg./100 ml., with a serum creatinine of 1.19 mg./100 ml. Urine had a specific gravity of 1.016, and contained 3 plus albumin. For the next 12 days, the patient was given frequent transfusions, despite a hematocrit of 35, in an attempt to maintain renal blood flow. In this period his serum creatinine rose to 3.7 mg./100 ml., while urine volume remained between 300 and 400 ml./day, with a concentration of only 350 to 370 milliosmolal. The patient then became even more deeply jaundiced, and urine volume decreased to less than 100 ml./day. He lapsed into deep coma and died three days later, with a serum creatinine of 4.6 mg./100 ml. Serum sodium concentration remained unchanged at 123 to 127 mEq./L. throughout his entire course, while blood pressure decreased to 90/60 mm. Hg during the period of renal failure. In the few days before death the stool guaiac test became positive for the first time.

In summary, this patient had a relatively short history of symptomatic liver disease, and entered with ascites and marked jaundice. As jaundice increased he developed renal failure and died in hepatic coma within two weeks of the onset of renal failure.

# Remaining four patients in Group III:

Clinical and laboratory features:

- 1. Age: 35-65.
- 2. Duration of symptomatic liver disease: one week to two years.
- 3. Ascites: minimal in two, moderate in one, marked in one.

- 4. Peripheral edema: absent in one, minimal in two, marked in one.
- 5. Initial serum bilirubin concentration: 4, 23, 30, 34 mg./100 ml.
- 6. Urine: acid; three had albuminuria; two had microscopic hematuria.

Course of renal failure: In two patients, urinary concentration was maintained for at least several days after the onset of azotemia. Subsequently, concentrating ability was impaired. Blood pressure decreased in all patients as renal failure developed. Death occurred from three days to three weeks after renal failure was observed, with maximal serum creatinine varying from 2.2 to 13 mg./100 ml. Serum sodium concentration varied from 120 to 128 mEq./L., and in three instances was unchanged from the values obtained before the onset of renal failure. Hepatic coma developed in three patients before death.

Group IV—Miscellaneous—five patients. One patient in this group had a blood nonprotein nitrogen of 20 mg./100 ml. and a urine specific gravity of 1.020 one month before the onset of renal failure. One week after the surgical repair of an umbilical hernia unaccompanied by hypotension, excessive blood loss or shock, the patient developed renal failure and in less than two weeks died with a nonprotein nitrogen of 66 mg./100 ml. and a serum bilirubin concentration of 1.6 mg./100 ml.

Of the remaining four patients, there was no apparent event in the clinical course which might be related to the onset of renal failure. However, in two instances we do not believe that the possibility of occult gastrointestinal bleeding has been adequately excluded.

One patient, age 68, entered in coma of unknown duration. He had minimal ascites, no edema, a serum bilirubin of 1.6 mg./100 ml., serum sodium of 140 mEq./L., urine specific gravity of 1.017, with a trace of albumin, and a normal electrocardiogram. Blood nonprotein nitrogen was 84 mg./100 ml., with a serum creatinine of 3.5 mg./100 ml. The patient was severely oliguric after admission, and died within 24 hours. Postmortem examination was unremarkable except for evidence of chronic Laennec's cirrhosis.

Another patient, aged 58, had had an abdominal paracentesis performed five months earlier, without apparent ill effect, although no studies of renal function are available. Three months before death, endogenous creatinine clearance was 60 ml./min., and urinary concentration, 700 milliosmolal, with a poor diuretic response to administered water. One month before death, serum creatinine concentration was 0.69 mg./100 ml. One week before death, the patient was observed to be lethargic and oliguric. Serum bilirubin was 4.0 mg./100 ml., the same as on admission, and serum sodium was 130 mEq./L., urine specific gravity was 1.022, and serum creatinine was 2.0 mg./100 ml. The patient died in hepatic coma one week later.

Another patient, aged 67, had marked ascites and a serum bilirubin of 1.6 mg./100 ml., serum creatinine of 0.84 mg./100 ml. (creatinine clearance, 60 ml./min.), and urine concentration greater than 700 milliosmolal. Two weeks later, without bleeding, paracentesis or increased serum bilirubin, his serum creatinine was 1.17 mg./100 ml. (creatinine clearance, 37 ml./min.), and inulin clearance, 33 ml./min., but urine concentration was 650 milliosmolal. Within two weeks the patient died in coma, with a serum creatinine of 2.2 mg./100 ml., and urine concentration of 540 milliosmolal without bleeding or change in serum bilirubin concentration.

Another patient, aged 35, is of special interest since his renal manifestations were unique. This patient had had jaundice and ascites for seven months before transfer to this hospital. He had no blood in his stool, and the serum bilirubin concentration remained 15 mg./100 ml. during the entire three weeks' hospitalization before death. He was never anuric (urine volumes approximated 1,000 to 2,500 ml./day) despite a rising serum creatinine, which reached 3.5 mg./100 ml. at the time of death. However, urine concentration approximated 300 milliosmolal and he had persistent 3- to 4-plus albuminuria, with a serum albumin concentration varying from 1.0 to 1.5 gm./100 ml. The question of concomitant nephrotic syndrome was raised in this patient. Aside from bile staining, the kidneys were normal histologically, thus probably excluding the usual common causes of the nephrotic syndrome in the adult, particularly glomerulonephritis.

We may now summarize certain features of our group of 22 patients as a whole:

### A. Clinical

1. The duration of symptomatic liver disease did not correlate with the development of renal failure.

2. Renal failure often developed with great rapidity.

3. Ascites varied from minimal to marked.

4. Jaundice varied from minimal to marked, and was actually decreasing in three patients when they developed renal failure.

5. Blood pressure decreased in all 22 patients.

6. Hepatic coma developed in 16.

7. All patients died.

# B. Laboratory

1. The urine was acid, and often contained albumin and hyaline and granular casts, as well as red blood cells.

2. In several instances the scanty urine was quite concentrated early in the course of renal failure. Certain patients had marked impairment in the ability to elaborate a strongly concentrated urine before death; others died with the urine still well concentrated. Other patients were observed never to have a significantly concentrated urine once renal failure had developed. Two patients with poorly concentrated urine had no period of oliguria while they had progressive azotemia.

3. Decreased glomerular filtration rate was documented with measurement of endogenous creatinine clearance and, in several instances, with inulin clearance. The clearance of para-aminohippuric acid was reduced in all patients in whom this function was determined.

4. The highest blood nonprotein nitrogen observed was 188 mg./100 ml. (creatinine, 14.3 mg./100 ml.). Death occurred, however, with the blood nonprotein nitrogen as low as 55 mg./100 ml., and serum creatinine concentration as low as 2.2 mg./100 ml.

5. Serum bicarbonate varied from 12 to 19 mMol./L. in most patients, was 8 mMol./L. in one, and within normal range in two.

6. Serum sodium concentration was generally reduced.

 Except for bile staining and occasional minimal tubular cell flattening, the kidneys examined histologically (18 patients) were essentially normal.

8. The histologic appearance of the liver reflected the spectrum of Laennec's cirrhosis, without any apparent predominance of one phase of the cirrhotic process.

#### DISCUSSION

The general problem of the relationship of the kidney to diseases of the liver has been considered in detail elsewhere,<sup>2</sup> and will not be reviewed here except as related to the specific issue of renal failure in the course of Laennec's cirrhosis of the liver. In this regard, our clinical observations are for the most part consistent with certain features of the nine patients in terminal liver failure described by Hecker and Sherlock.<sup>3</sup> In addition, our experiences with therapeutic endeavors confirm certain of the observations reported by these investigators.

Although the present study does not exclude the possibility of transient, reversible renal failure in cirrhosis, it is apparent that the development of azotemia in the course of Laennec's cirrhosis of the liver may be of grave prognostic significance. However, the reason for the poor prognosis is not at all clear. Certainly, greater degrees of renal failure are perfectly consistent not only with life but also with an active, productive existence in many patients with primary renal disease. It is possible, of course, that the patient with a damaged liver may be more sensitive to certain "toxic" products resulting from diminished renal function. Nonetheless, one must raise the question whether death in these patients is related to the renal failure at all, or whether the renal failure is merely a reflection of a more fundamental adverse turn of events. Incidentally, a number of the patients reported here had a poor diuretic response to administered water several months prior to their deaths, at a time when other parameters of renal function were within normal limits, thus confirming previous observation that this abnormality has prognostic importance.4

While the mechanism of the renal functional impairment in cirrhosis cannot be derived from these observations, we may draw certain descriptive conclusions. First, it seems apparent that renal failure in cirrhosis is not the result of protracted and progressive deterioration of kidney function, despite the fact that two patients were known to have a slightly-reduced glomerular filtration rate a few months before the onset of renal failure. In most instances we have observed patients with normal blood nonprotein nitrogen, normal glomerular filtration rate, and good urinary concentration a matter of a few months, a few weeks, and indeed even days before they manifested decreased filtration rate and azotemia. Consequently, it would seem that the causative factors must be sought among circumstances that

can produce acute or subacute renal dysfunction with little disturbance in the histologic appearance of the kidney.

A number of our clinical and laboratory observations further suggest that we might well search primarily for factors adversely affecting the renal circulation. As we have already indicated, some of the patients maintained the capacity to elaborate a concentrated acid urine and excrete phenolsulfonphthalein normally early in the course of renal failure, and as the period of observation was prolonged, impairment of concentrating power sometimes ensued. This combination of reduced glomerular filtration rate and a scanty concentrated urine, with progression to impaired urinary concentration, is reminiscent of the findings in severe circulatory shock. That none of the patients in the present series had obvious clinical shock does not preclude the possibility of a qualitatively similar mechanism operating to reduce renal blood flow. Such a thesis would be consistent with the fairly abrupt onset of renal failure described; with the apparent precipitation by paracentesis, when extracellular fluid is removed: with the onset after gastrointestinal bleeding, even of a mild degree, and with the reduction in blood pressure. The lack of an observed oliguric phase in two patients is not necessarily inconsistent, in view of the fact that patients with acute tubular damage due to other causes may never have an observed oliguric phase, and may excrete a frankly dilute urine while the blood nonprotein nitrogen increases.<sup>5</sup> Finally, the lack of impressive changes in the histologic appearance of the kidney (as well as the occasionally reported cases of tubular necrosis in terminal cirrhosis 6) is consistent with this suggestion.

The mechanisms by which impairment in glomerular filtration rate and renal blood flow may develop in patients with cirrhosis is not clear, and it is in this direction that our present investigative efforts are mobilized. It is possible that some material, either formed in the diseased liver or not detoxified by it, may result in reduced renal blood flow.7-10 The possibility also exists that a decrease in the extracellular fluid volume in some critical portion of the body, or what is called the "effective extracellular volume," may account for the decreased renal plasma flow.2 These alternatives are conjectural at this time. Obviously, other possible causes of diminished renal blood flow may exist and may be of great importance. As suggested above, renal failure may be only a part of a broader lethal event. In this context, a reduction in renal blood flow may be the result of the same factors which produced the observed decreased cerebral 11 and hepatic blood flow 8 in advanced cirrhosis. These factors remain unknown. All we can say with confidence at the moment is that the decreased renal blood flow is not secondary to a reduction in cardiac output, since three patients in renal failure (with reduced inulin and para-aminohippuric acid clearances) were found to have an increased cardiac output.12 The high cardiac output in cirrhosis is thought to be due to profound peripheral vasodilatation. 18, 14 Indeed, we have repeatedly observed a warm skin over the abdomen in some

patients. Less often, an area of erythema over the abdomen is also observed. It is possible that, in some patients, these areas become so dilated that the increased cardiac output cannot provide blood to vital organs, including the kidney.

However, the hypothesis regarding the importance of the renal circulation in this syndrome, as distinguished from renal parenchymal disease, may prove incorrect when more facts are available. Indeed, there really is no reason to assume that there is only one common mechanism for the development of renal failure in cirrhosis.

Since hyponatremia may be associated with renal failure in other conditions, this factor warrants consideration as a possible cause of the terminal renal failure. In view of the following facts, it seems improbable that the hyponatremia exercises a primary function. First, hyponatremia of comparable degree is common in patients with cirrhosis without renal failure. Second, in the patient with cirrhosis and terminal renal failure, the serum sodium concentration may be no lower than during an asymptomatic period. Third, in some instances, nonprotein nitrogen elevation has been documented prior to any significant reduction in serum sodium concentration. Finally, correction of the depressed serum sodium concentration under these circumstances fails to result in improvement.

While potassium deficiency may exist in patients with cirrhosis, it probably plays little if any role in the development of renal failure. Kaliopenic nephropathy is characterized by disturbance in the capacity to elaborate a concentrated urine, 15 whereas azotemia may develop in cirrhosis while the urine remains concentrated.

It is quite apparent that our treatment of renal failure in cirrhosis is grossly inadequate.

In the past, restricting fluid and salt intake to equal daily losses has not altered the course favorably. Abdominal paracentesis has been carried out to improve renal function by reducing the effects of increased intra-abdominal pressure. If such an advantage can accrue to a patient with cirrhosis, it must be weighed against the possible adverse effects of reducing the extracellular volume. It is apparent from the present observation, and others, that renal failure may actually be precipitated by abdominal paracentesis. In our opinion at present, this may well be a potentially hazardous procedure, *especially* in the patient with a poor diuretic response to administered water. This is currently being studied further.

With the possibility that the diminished flow of blood to the kidney and reduced glomerular filtration rate may be important factors in the development of renal failure, we have made attempts to expand the circulation with saline, dextran and whole blood transfusions. In one patient, glomerular filtration rate increased from 30 to 60 ml./min. after saline administration. Thereafter, daily saline administration failed to maintain the increased filtration rate and resulted in more ascites, to the point of discomfort.

The administration of saline in other patients was not associated with any definite improvement. Dextran infusions were given to two patients with no alteration in the clinical situation or the measured renal function. Daily whole blood transfusion in two patients may have been accompanied by a slower progression of renal failure. However, this was difficult to assess. At any rate, the ultimate course of events was unaffected. In one patient we observed a *transient* increase in urine volume and glomerular filtration rate following noradrenalin, thus confirming the results of Hecker and Sherlock.<sup>8</sup> While it is apparent that our efforts have been unsuccessful so far, we are continuing to carry out physiologic and clinical studies under these conditions.

### SUMMARY

We have presented a group of 22 patients with alcoholism and cirrhosis of the liver who developed renal failure and died. Nine patients developed renal failure after mild gastrointestinal bleeding, three after abdominal paracentesis, five while jaundice was severe or progressive, one after surgery, and four without apparent precipitating factors. The mechanism of this syndrome remains unclear, although we propose that the present observations, both clinical and laboratory, are most consistent with the presence of reduced glomerular filtration rate and renal blood flow, rather than with renal parenchymal disease. The cause of the diminished blood flow to the kidneys is not known, but may well be a factor of broader significance, resulting in impaired circulation to other vital organs as well as to the kidney. It is not established that renal failure per se is the cause of death in most instances. Therapy is presently unsuccessful. We are continuing our inquiry into the mechanism of renal failure in cirrhosis in the hope that better understanding of the disturbed physiology in cirrhosis may result, and that a therapeutic approach to this problem may be derived.

### ACKNOWLEDGMENTS

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#### SUMMARIO IN INTERLINGUA

Le facto que disfallimento renal pote supervenir in le curso de cirrhosis hepatic de Laennec es cognoscite depost multe annos. Iste phenomeno es inter le conditiones que es laxemente designate como le "syndrome hepatorenal," sed pauco es cognoscite con respecto a su etiologia, pathogenese, curso clinic, o therapia.

Le presente reporto se restringe al analyse de 22 casos de cirrhosis de Laennec in que disfallimento renal se disveloppava. Le sequente constatationes esseva facite.

Novem del patientes disveloppava disfallimento renal post leve episodios de sanguination gastrointestinal que non esseva satis marcate pro causar un reduction significative del hematocrite o evidentia clinic de choc. In tres le disfallimento occur-

reva post paracentese abdominal, in cinque durante que le ictero esseva sever o progressive, in un post un intervention chirurgic, e in quatro sin apparente factor precipitatori. Le disfallimento renal superveniva frequentemente con extreme rapiditate. In multe casos, normal functiones renal esseva observate menses o septimanas o mesmo dies ante le declaration de azotemia. Ascites variava inter minimal e marcate. Le mesmo vale pro ictero. In tres patientes, le ictero de facto recedeva quando le disfallimento renal se disveloppava. Le tension de sanguine descendeva in omne le patientes. Coma hepatic occurreva in 16. Omne le 22 moriva.

Le urina esseva acide. Frequentemente illo contineva albumina, cylindros hyalin e granular, e etiam erythrocytos. In plures del patientes, le micre amonta de urina producite esseva concentrate durante le phases initial del disfallimento renal. Certes perdeva le capacitate de elaborar un urina concentrate ante lor morte. Le valores del clearance de inulina e de para-aminohippurato esseva reducite in omne le patientes pro qui illos esseva determinate. Durante que le plus alte valor pro nitrogeno non-proteinic del sanguine esseva 188 mg pro 100 ml, multo plus basse valores esseva notate al tempore del morte. Le minime tal esseva 55 mg pro 100 ml, e le concentration minimal de creatinina in le sero esseva 2,2 mg pro 100 ml. Le concentration de natrium in le sero esseva generalmente reducite. A parte le presentia de coloration biliari e un applattimento minimal de cellulas tubular, le renes esseva histologicamente normal.

Durante que le pathogenese del disfallimento renal remane obscur, le rapiditate de su disveloppamento suggere que illo es de natura acute o subacute. Le sequentia, observate in certe patientes, de bon capacitate concentratori de urina al initio del curso del disfallimento renal, sequite per disturbation del concentration urinari, pare le plus compatibile con un reduction del fluxo renal de sanguine como causa del syndrome. Iste notion es supportate additionalmente per le apparente precipitation de disfallimento renal per leve episodios de sanguination gastrointestinal o paracentese abdominal e similemente per le presentia uniforme de un reduction del tension de sanguine.

Le causa del reducite provision de sanguine al renes non es cognoscite, sed il es possibile que il se tracta de un factor de signification plus general le qual effectua un defective circulation etiam in altere organos vital e non solmente in le ren. Nulle prova existe a iste tempore que disfallimento per se es le causa del morte. Currentemente un therapia efficace non es disponibile.

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# THE INCIDENCE OF MYOCARDIAL INFARCTION IN PORTAL CIRRHOSIS\*

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THERE is a widely circulated statement that alcoholics rarely die of coronary atherosclerosis. Despite this general impression, the small amount of data available does not substantiate this belief. Since it is often impossible to obtain reliable information concerning alcohol consumption, a more objective criterion was sought in the form of cirrhosis of the liver. While it is true that portal cirrhosis is associated with a variety of conditions, a major concomitant is alcoholism.

Previous work 2 consisted of a study of the incidence of coronary arteriosclerotic changes in cirrhotic patients. Unfortunately, the noncirrhotic control group with which they were compared was prepared by a different investigator and drawn from a different population. Another investigation 8 correlated the degree of generalized arteriosclerosis in cirrhotics with that in a control group, and found less arteriosclerosis in the cirrhotics.

In this present study, those subjects with portal cirrhosis verified grossly and microscopically at necropsy were regarded as cirrhotics. To provide a completely objective criterion for coronary atherosclerosis, only those patients dying of acute myocardial infarction demonstrated at autopsy were included. Rigidity in the establishment of these criteria reduced the number of subjects in the study. However, it prevented the uncertainties introduced by attempts to evaluate clinically the degree of atherosclerosis, or to decide whether a patient could be regarded as having portal cirrhosis from laboratory findings and history alone.

#### MATERIALS AND METHODS

All autopsy material was derived from records of the Veterans Administration Hospital in Coral Gables, Florida, from 1953 to 1957. Only male patients were used, since so few females were present. A total of 1,373 autopsied cases was examined; of these 129 were Negroes. Only cases of verified portal cirrhosis were studied and the number of these cirrhotics dying of acute myocardial infarction observed. In a corollary

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TABLE 1
Distribution of Coronary Disease and Cirrhosis in Selected and General Autopsy Populations

Type of Population	Number of Cases	Mean Age		of Coronary sease		of Portal
			No.	%	No.	%
Coronary disease Cirrhosis All autopsies	156 123 1373	60.2 53.7 57.7	156 4 156	100.0 3.3 11.4	123 123	2.6 100.0 8.9

survey, all cases of fatal coronary artery occlusion with myocardial infarction were examined for verified portal cirrhosis.

#### RESULTS

Of 1,373 autopsied cases, irrefutable evidence of true portal cirrhosis was found in 123, and almost all of these gave a history of heavy alcohol consumption. Of this number of cirrhotics only four individuals (3.3%) died of acute coronary occlusion with myocardial infarction.

On the other hand, of the 1,373 autopsied cases, 156 gave gross and microscopic evidence of having died of coronary occlusion with myocardial infarction. Thus, in the total autopsy population of this hospital, 11.4% died of myocardial infarction, while only 3.3% of those cases showing portal cirrhosis died of this disease. These figures are shown in table 1.

Table 1 shows that the average age of the coronary group was about 60, and that of the cirrhotic group was 53. The age distribution by decades in these two selected groups and in the general autopsy population is shown in table 2.

To determine whether the lower incidence of coronary disease in the cirrhotics could be explained by age alone, table 3 was prepared. On the basis of the incidence of coronary disease by decades (table 2), a calculation was

TABLE 2

Age	Cirrhosis No.	Cirrhosis %	Core	onary	Total A	utopsies
Age Cirrnosis No.	Curuosis 70	No.	%	No.	%	
11-20	0	0.0	0	0	5	0.4
21-30	1	0.8	0	0	38	2.8
31-40	16	13.0	8	5.1	118	8.6
41-50	31	25.2	17	10.9	162	11.8
51-60	43	35.0	48	30.7	388	28.2
61-70	24	19.5	48 58	37.2	475	34.6
71-80	6	4.9	22	14.1	148	10.8
81-90	2	1.6	3	1.9	37	2.7
91-100	0	0	0	0	2	0.1
	123	100.0	156	99.9	1373	100.0

TABLE 3

The Occurrence of Coronary Occlusion with Mycardial Infarction in Patients with Portal Cirrhosis

			Calculated Incidence
Age		Observed Incidence	Expected number of coronary attacks on the basis of incidence by age (table 3)
31-40		0	1.1
41-50		0	3.3
51-60		2	5.3 .
61-70	1	- 1	2.9
71-80		. 1	0.9
81-90		. 0	0.1
		4	13.6

made of the number of myocardial infarctions which might be expected in the cirrhosis group. This calculated incidence of coronary disease in cirrhotic patients is compared with the observed incidence. It is noted that, whereas 13.6 cases were predicted on the basis of age alone, actually only four cases were observed.

The incidence of old (or healed) myocardial infarctions is of interest. Twenty-four old myocardial infarctions were observed in the 123 cases of portal cirrhosis, whereas in the 156 autopsied patients dying with acute myocardial infarction, 133 demonstrated prior (old) infarction. Therefore, while a significant number of patients with portal cirrhosis had experienced a myocardial infarction (19.5%), few died as a result of this. It was apparent from an examination of autopsy records that infarction in the cirrhotic group was infrequent in the lungs, spleen, kidney and brain, as well as in the myocardium. The incidence of infarcts in organs other than the heart in the cirrhotic group was compared with that found in the coronary group, and is shown in table 4. It will be seen that in every organ both healed and fresh infarcts, when differentiated, were more frequent in the group of patients dying of coronary occlusion with myocardial infarction. Table 5 outlines the incidence of various pathologic lesions in 156 coronary patients and in 123 patients with portal cirrhosis. In the lungs, emphysema and fibrosis were more frequent in the coronary group. As anticipated, the

TABLE 4
Frequency of Infarctions in Various Organs

Site	Coronary Occlusion with Acute Myocardial Infarction 156 Patients	Portal Cirrhosis 123 Patients
Pulmonary embolism	477	
with infarction	1/	3
Spleen infarction	6	- 2
Kidnev		
Old infarction	12	0
Acute infarction	8	0
Brain-infarction	10	3
Coronary		
Old infarction	133	24
Acute infarction	156	4

TABLE 5 Comparison of Pathologic Findings Demonstrated at Autopsy in the Coronary and Cirrhotic Groups

in the Coronary and Cirr	hotic Groups	
	Coronary Group	Cirrhotic Group
Lungs	Group	Oloup
Pulmonary arteriosclerosis	6	6
Emphysema	52	26
Fibrosis	19	10
Cardiovascular		
Pericarditis	14	4
Hypertrophy	70 34	38
Myocardial aneurysm Coronary atherosclerosis—mild	1	48
severe	146	19
Aortic atherosclerosis—severe	137	46
Aneurysm, great vessels	5	1
Prostate		
Hyperplasia	113	46
Prostatitis—	3	7
carcinoma latent carcinoma	9	6
Esophagus		
	1	50
Erosions Varices	0	73
	0	
Stomach and duodenum		4.5
Ulcers Gastritis	5 2	15 5
	4	9
Colon		
Diverticula Parillemente	13	5 5
Papillomata	3	3
Gall-bladder		
Stones	7 4	8 7
Cholecystitis	4	,
Spleen		
Extramedullary hematopoiesis	0 .	4
Enlarged Fibrosis	9	64 53
	0	00
Liver		
Fatty infiltration	30	11
Cirrhosis, Laennec's Carcinoma, primary	0	9
Kidney	425	470
Arteriosclerosis Arteriolosclerosis	135 45	47 23
Pyelonephrosis	11	7
Pancreas		
	0	8
Acute pancreatitis Fatty infiltration	33	14
Fibrosis	.4	13
Atherosclerosis of vessels	4	1
Thyroid		
Goiter	13	5
Testis		
Atrophy	61	85
ratiophy	01	00

incidence of esophageal varices and erosions, splenic enlargement and fibrosis and testicular atrophy was greatly increased in cirrhosis. Similarly, the high incidence of severe atherosclerotic disease of the aorta and kidneys, pericarditis, myocardial hypertrophy and aneurysm might be expected in patients dying with acute myocardial infarction. Fatty infiltration of both liver and pancreas was observed more frequently in those patients dying of coronary artery disease.

#### DISCUSSION

The results indicated that, in our autopsied hospital population, individuals with portal cirrhosis suffer fatal coronary occlusion with myocardial infarction less frequently than do noncirrhotics. Obviously a variety of factors may be involved.\* Part of the explanation is undoubtedly the younger age of the cirrhotic patient. However, we were unable to account for the entire difference by age alone, as indicated in table 3. It would appear that the cirrhotics manifested less tendency to develop infarction in the lung, brain, spleen and kidney, as well as in the myocardium. Such a finding suggests a systemic rather than a localized vascular or organ change.

It is recognized that there is less atherosclerosis in prolonged wasting disease,<sup>4</sup> and that malnutrition may be associated with portal cirrhosis. This cannot be disregarded, even though the cirrhotics in our series were not generally underweight at autopsy.

One may speculate on the importance of certain factors regarded as having some relationship to atherosclerosis. The heightened estrogen titer in the cirrhotic is known, and may be manifested at autopsy by such findings as premature testicular atrophy. Estrogens have long been regarded as antiatherosclerotic agents, and may therefore protect the cirrhotic patient.

Less well defined is the function of clearing factor or lipoprotein lipase. This enzyme, which clears postprandial lipemia, is diminished in coronary disease, 6 and has recently been reported to be increased in cirrhosis. 7 Para-

\*The possibility that our autopsy population was drawn from a group not representative of the general population might suggest that the Berkson-Mainland fallacy 9 occurred to produce biased data. As a partial answer, a comparison has been made of the autopsy rates by disease of this Veterans Hospital and those of a large nearby civilian general hospital with both ward and private patients. To provide an accurate comparison with the group used in this study, only males over the age of 20 years were counted, with following results:

	V. A. Hospital 1953-1957	Jackson Memorial 1956
Total autopsies examined	1.373	346
Myocardial infarction	11.4%	12.1%
Portal cirrhosis	9.0%	8.1%

If autopsy rates by disease are biased as a result of abnormal selection in this hospital, one might expect that rates from two entirely different types of hospitals would vary considerably. Such variation could be dependent upon a number of factors, including the socio-economic status of the hospital clientele. It will be noted that the incidence at autopsy of myocardial infarction and cirrhosis of the liver was essentially the same for the two hospitals.

doxically, however, the administration of large quantities of alcohol has been reported to produce lipemia.8

Serum cholesterol values in the survivors of myocardial infarction have been shown to be elevated,<sup>5</sup> and are often within normal levels or below <sup>7, 2</sup> in portal cirrhosis. This may be explained in part by inadequate diet or by the inability of impaired liver to promote absorption or synthesis of cholesterol.

#### SUMMARY

Of 123 patients with portal cirrhosis verified at necropsy, only 3.3% died of acute coronary occlusion with myocardial infarction. In the general autopsy population of 1,373 patients, 11.4% died with this condition. When 123 cirrhotics were compared with 156 cases of death by coronary occlusion with myocardial infarction, the incidence of infarction in other organs is much lower in the cirrhotic group. The relative frequency of other pathologic findings is also compared.

#### SUMMARIO IN INTERLINGUA

Al Hospital del Administration de Veteranos a Floral Gables in Florida, un studio necroptic esseva interprendite con respecto al incidentia de infarcimento myocardial in individuos con cirrhosis portal. Inter 123 casos de necropticamente confirmate cirrhosis portal, solmente 3,3% concerneva patientes morte ab acute occlusion coronari con infarcimento myocardial. In le population necroptic general, consistente de 1.373 subjectos, 11,4% habeva morite ab ille condition. Quando 123 cirrhoticos esseva comparate con 156 subjectos morte ab occlusion coronari, le incidentia de infarcimentos de pulmon, cerebro, splen, e ren esseva plus base in le gruppo cirrhotic. Esseva etiam comparate le frequentias relative de altere constatationes pathologic.

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## CASE REPORTS

# BLASTOMYCOSIS MENINGITIS: REPORT OF A CASE SUCCESSFULLY TREATED WITH AMPHOTERICIN B\*

By Everett J. Carmody, M.D., and William Tappen, M.D., San Diego, California

NORTH American blastomycosis has been described as a chronic infectious disease characterized by suppurative lesions in the skin or subcutaneous tissue, but it may also involve the lungs, bones, genitourinary organs and the central nervous system, and is caused by a specific organism, *Blastomyces dermatitidis*. <sup>14</sup> Involvement of the central nervous system by this organism is quite rare.<sup>2, 7, 8, 10, 14, 16, 21, 24</sup> Our review of the English literature leads us to believe that the following case is the first reported of proved blastomycosis meningitis successfully treated with amphotericin B.

#### CASE REPORT

A 22 year old Negro male was referred to the San Diego County General Hospital on October 10, 1958, with a diagnosis of "cutaneous blastomycosis," proved by biopsy from a skin lesion.

Present Illness: About four years prior to admission the patient first noticed a small swelling on the right side of the neck just below the angle of the jaw. The patient described this lesion as a "pimple," which he would frequently squeeze, with the production of a whitish, cheesy material. Following this, the lesion would recede for a period of from four to five months, when it would recur. The patient paid little attention to it until four months prior to admission, when he noticed that it was becoming larger and beginning to spread. Two months later he was persuaded by a friend to seek medical advice for this "sore." He went to a physician's office in southern California where he was told that the lesion was a mole, and was treated with cauterization and salves. After a week of the above treatment without much change in the lesion, the patient went to another physician, who removed the eschar which had formed over the lesion and advised another salve as therapy. Twice that week the patient returned to the physician's office, where the lesion was debrided and salve applied. No change occurred in the appearance or size of the lesion. On his last visit the patient was complaining of frontal headache and stiffness of the neck. These symptoms were most prominent during working hours (from 10 a.m. to 9 p.m.), but seemed to recede when he arrived home. The following day the symptoms recurred and the cycle would repeat itself. He was treated with some "headache pills," without much benefit. Two weeks prior to his admission to the San Diego County General Hospital the patient was referred to a local dermatologist, who had

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the lesion biopsied. The pathologic diagnosis was a granuloma of the skin of the right mandible due to blastomycosis. The patient was subsequently referred to this Hospital

Past History: The patient was born in Arkansas, the oldest boy in a family of six boys and four girls. His father was a farmer. His early years were uneventful except for a case of pneumonia at the age of seven years, which was treated at home by a physician. His recovery was apparently uneventful. At the age of 10 he went to live with an uncle in Memphis, Tennessee, with whom he stayed for a period of seven years. During this time his health remained good. He obtained a part-time job as a mechanic's helper, and shortly thereafter moved out of his uncle's home, and worked in several garages in and around Memphis. About two and one-half years ago he came to California. While in San Diego he worked in several garages as a mechanic. Prior to his admission to the hospital the patient was employed by a car-wash station.

Physical Examination: On admission to the hospital the patient was a well developed, well nourished but slender Negro male in moderate distress because of headache and stiffness of the neck. Blood pressure was 130/70 mm. of Hg; pulse with normal sinus rhythm at a rate of 80 per minute; respirations, 20 per minute; temperature 100.8° F. The skin was warm and dry. The lesion over the right neck below the angle of the jaw measured 4 cm. by 1 cm. It was crusty, irregular, papulomatous and dry. There was a sharp demarcation from the surrounding normal skin. The central portion of the lesion was atrophic, with whitish scarring present. With the exception of moderate nuchal rigidity, the remainder of the physical examination was completely negative.

Laboratory Findings: Hemoglobin, 15.5 gm.; hematocrit, 47%; white blood count, 9,600, with a differential count of 71 polymorphonuclears, 2 stab forms, 24 lymphocytes and 3 mononuclears. The sedimentation rate was 17 mm. in one hour (Westergren). A spinal puncture was performed on October 11, and the findings are listed in table 1.

The urine was entirely within normal limits. A culture of the facial lesion done on October 15 grew out only Staphylococcus aureus. Complement fixation on the serum was reported on October 22 as positive with a 1:16 titer for blastomycosis. Similar studies were negative for histoplasmosis and coccidioidomycosis. The blood urea nitrogen was 20 mg. %. Sputum and blood cultures were negative for fungi on several occasions. Subsequent spinal fluid examinations are listed in the table.

By November 21 the complement fixation on the serum was negative for blastomycosis. The complement fixation test for histoplasmosis and coccidioidomycosis remained negative.

Radiologic Reports: On November 14 the chest film was interpreted as showing considerable exaggeration of the hilar markings, especially on the left, where there was noticeable peribronchial thickening in the central lung field (figure 1). Otherwise the lung fields were essentially clear. The heart and great vessels were within normal limits. The findings of the left lung were considered to be consistent with a chronic granulomatous process. A bone survey was completely negative. Repeated films of the chest showed no change from the initial report (figure 2).

Course in Hospital: During the initial period of hospitalization the patient was treated symptomatically while awaiting the report on the spinal fluid. Despite the severity of his underlying disease, he did not appear to be acutely ill, but rather restless and drowsy. When the spinal fluid report was obtained (figures 3, 4), treatment was instituted with amphotericin B. Previous experience with the use of amphotericin B in the treatment of disseminated coccidioidomycosis by one of us (W. T.) formed the basis of the therapeutic program. The initial dose was 25 mg. dissolved in 1,000 c.c. of 5% distilled water, administered intravenously by slow

TABLE 1 Spinal Fluid Findings

	6		Smear			9	Chloride	Culture	Complement
Date	Fresures	Appearance	Cells	Organisms	Total protein	Sugar	CHIOING	Cantal	fixation
10/11/58	O. P. 186 mm./water F. P. 140 mm./water	Sl. turbid	447 wbc (22% polys,	Positive	110.6 mg. %	45 mg. %	% · Su 069	Positive for B. d.	
10/17/58	O. P. 200 mm./water F. P. 170 mm./water O. P. 220 mm./water	Sl. turbid Clear	Many wbc 60 wbc	Positive for B. d.	306 mg. % 42.4 mg. %	80 mg. %	750 mg. % 700 mg. %	750 mg. % Positive Negative for for B. d. B., C., H.* 700 mg. % Negative	Negative for B., C., H.
11/25/58	F. P. 180 mm./water O. P. 160 mm./water F. P. 110 mm./water	Clear	(4% polys, 96% lymphs) 51 wbc (5% polys,	Negative	36 mg. %	67 mg. %	725 mg. %	36 mg. % 67 mg. % 725 mg. % Negative for B., C., H.	Negative for B., C., H.
12/12/58		Clear	95% lymphs) 43 wbc (10% polys,	Negative	58 mg. %	83 mg. %	790 mg. %	Negative	
1/5/59	O. P. 100 mm./water F. P. 80 mm./water	Clear	24 wbc (10% polys,	Negative	44.6 mg. %	115 mg. %	1	Negative	
2/16/59	O. P. 160 mm./water F. P. 120 mm./water	Clear	6 wbc (100% lymphs)	Negative	37.9 mg. %	74 mg. %	725 mg. 9,	725 mg. % Negative	

Opening pressure Final pressure Blastomyces dermatitidis

\*0.F. B. d. P.

B. Blastomycosis C. Coccidioidomycosis H. Histoplasmosis drip over a six-hour period. As we anticipated reactions to the drug, the patient was given 50 mg. of Benadryl by mouth before the infusion, and another 50 mg. were added to the infusion fluid. About an hour after the infusion was started the patient developed frank chills, which were treated with the addition of blankets to the bed,

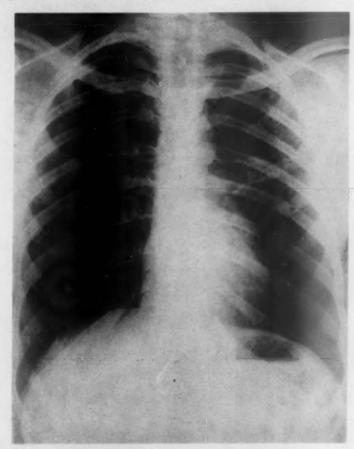


Fig. 1. Admission roentgenogram of chest.

and aspirin compound. This measure seemed to comfort the patient, and he took the rest of the infusion without further incidents. The program of administered dosage is outlined in table 2.

Since we were unable to find any similar cases reported in the literature, we decided to increase the dosage of the amphotericin B gradually, according to the patient's tolerance, until we had reached a level of 75 mg. (1.25 mg./Kg.) per infusion per day. During the early stages of the treatment the only side-effects of the medication were chills and occasional nausea. With continued therapy these side-effects diminished. A blood urea nitrogen test was done biweekly and its level was used as a rough guide in stopping or increasing the medication. On October

28, after the patient had received a total of 400 mg. of amphotericin B, his temperature, which had been slightly elevated to this point, returned to normal and remained there during the rest of the hospitalization. He was now free of headache and stiffness of the neck, but became quite anorectic. He was placed on a liquid diet, with added protein feedings between meals. The blood urea nitrogen had risen

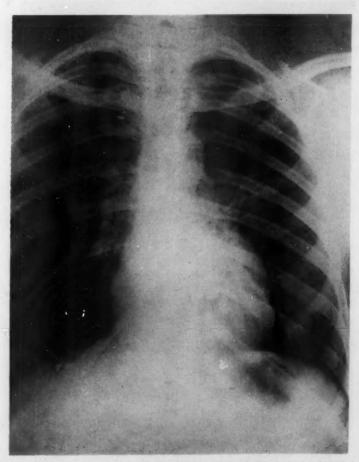


Fig. 2. Roentgenogram of chest on discharge from the hospital, showing little change from the initial film.

from 20 mg.% to 36 mg.% at this time, with a creatinine of 2.2 mg.%. It was deemed advisable to omit the medication for a day or two and encourage fluids. Two days later the blood urea nitrogen had dropped to 17 mg.% and the medication was reinstituted. On November 5 the patient appeared to be significantly improved, although he was still a feeding problem. Serious consideration was given to instituting tube feeding, but the patient spontaneously improved his fluid intake at this time.



Fig. 3. Photomicrograph of smear made from spinal fluid culture, showing round and pyriform conidia found in filamentous stage. ( $\times$  450.)

We were constantly running into trouble trying to find veins for the infusion fluid. Most of his available veins were now thrombosed. The long duration for the infusions made his arms very painful. In an attempt to relieve some of the discomfort for the patient, the infusion was allowed to run in about four hours instead of the previous six hours. No increased reactions occurred.

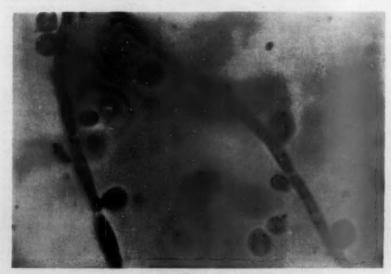


Fig. 4. Same as figure 3.  $(\times 970.)$ 

On November 13 the skin lesion was completely healed (figure 5). The patient was now bright and talkative. His only complaint was that he didn't like the "needles." He continued to show improvement. Now on a regular diet, he was asymptomatic and ambulatory about the ward. On several occasions during his illness a blastomycosis skin test with the 1:100 strength solution was negative. On

TABLE 2

Date	Medication	Dosage	BUN	Reaction	Remarks
0/19/58	Amphotericin B	25 mg.		F. C.:T. 99.8° F.	Satisfactor
0/20/58	Amphotericin B	25 mg.	20 mg. %	C. S.: T. 99.0° F.	Satisfactor
0/21/58	Amphotericin B	35 mg.	. 10	C. S.:T. 99.0° F.	Satisfactor
0/22/58	Amphotericin B	40 mg.		C. S.:T. 99.4° F.	Satisfactor
0/23/58	Amphotericin B		27 mg. %	C. S.; T. 99.8° F.	Satisfactor
0/24/58	Amphotericin B	35 mg.	2. mg. 70	C. S.: T. 101° F.	Satisfactor
0/25/58	Amphotericin B	50 mg.		C. S.: T. 100.8° F.	Satisfactor
0/26/58	Amphotericin B	65 mg.		C. S.:T. 99.8° F.	Satisfactor
0/27/58	Amphotericin B	75 mg.		C. S.:T. 100° F.	Satisfactor
0/28/58	1 mpnotonem 15		36 mg. %	0.0	- Curimino to
thru	Omit therapy		30 mg. 70	T. 98.6° F.	
0/30/58	Omit therapy		17 mg. %	1. 30.0 1.	11
0/31/58	Amphotericin B	75 mg.	17 mg. 70	C. S.: T. N.	Satisfactor
1/1/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
1/2/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
1/3/58	Amphoterich B	ro mg.	36 mg 01	C. S. 1. 11.	Satisfactor
thru	Omit therapy		36 mg. %		
1/4/58	Omit therapy				
1/5/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
1/6/58	Amphotericin B	75 mg.	26 01	C. S.:T. N.	Satisfactor
1/7/58			36 mg. %	C. S.: T. N.	Satisfactor
	Amphotericin B	75 mg.	-	C. S.: T. N.	Satisfactor
1/8/58	Amphotericin B	75 mg.		C. S.:T. N.	
1/9/58	Amphotericin B	75 mg.			Satisfactor
1/10/58	Amphotericin B	75 mg.			Satisfactor
1/11/58	Amphotericin B	75 mg.		C. S.: T. N. C. S.: T. N.	Satisfactor
1/12/58	Amphotericin B	75 mg.	22 01	C. S.:T. N.	Satisfactor
1/13/58	Amphotericin B	75 mg.	32 mg. %	C. S.: T. N.	Satisfactor
1/14/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
1/15/58	Amphotericin B	75 mg.			Satisfactor
1/16/58	Amphotericin B	75 mg.	26 00	C. S.:T. N.	Satisfactor
1/17/58	Amphotericin B	75 mg.	36 mg. %	C. S.:T. N.	Satisfactor
1/18/58	0 4 4	11 3			1
thru	Omit therapy				
1/19/58		in a		C C . T N	6.00
1/20/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
1/21/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
1/22/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
1/23/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
1/24/58	Amphotericin B		31 mg. %	C. S.:T. N.	Satisfactor
1/25/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
1/26/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
thru	Home for holiday			22.2	
2/1/58	Amphotericin B	75 mg.	Marie II	C. S.:T. N.	Satisfactor
2/2/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
2/3/58	Amphotericin B		17 mg. %	C. S.:T. N.	Satisfactor
2/5/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
2/8/58	Amphotericin B	75 mg.		C. S.:T. N.	Satisfactor
2/11/58	Amphotericin B	75 mg.		C. S.: T. N.	Satisfactor
2/13/58	Amphotericin B	75 mg.	and the	C. S.: T. N.	Satisfactor
2/15/58	Patient discharged		Carlo III		
	to Clinic				

Total dosage: 2,650 mg. (2.65 gm.) over a 57-day period.
\* F. C. Frank chills. C. S. Chilly sensations. T. N. Temperature normal.



Fig. 5. Healed cutaneous lesion.

December 15, 66 days after his admission, the patient was discharged from the hospital to be followed in the Outpatient Clinic. To date he has been seen every two weeks in the clinic by one of us (E. C.) and remains completely asymptomatic. He has gained about 10 pounds in weight since his discharge (130 to 140.5 pounds). The skin lesion has healed with a keloid residual.

Comment: North American blastomycosis was formerly considered to exist in two specific forms, cutaneous and systemic. In 1951 Schwarz and Baum 20 proposed that the disease was predominantly a pulmonary infection, and that its cutaneous manifestations were secondary to the systemic involvement. Wilson et al.25 stated in 1955 that the form of blastomycosis previously designated as cutaneous, and attributed to direct inoculation of the organisms into the skin, should now be considered to be only another manifestation of the disseminated form of the disease, originating in most instances from a previously unrecognized primary pulmonary focus. The case presented may well fit into the above classification. Although the first manifestation of the disease was in the skin, the underlying pulmonary involvement may well have been present for some time before the appearance of the cutaneous lesion.

The diagnosis of blastomycosis can only be suspected from the clinical picture alone. A definitive diagnosis must depend on the laboratory findings. The organisms should be positively identified on a direct smear of the material removed from the suspected lesion. Cultures must be positive when grown on proper medium, and the histopathologic picture should be characteristic on tissue section. The present case fulfills all of these criteria.

In their review of the literature in 1939, Martin and Smith <sup>16</sup> found 243 cases (proved and presumptive) of systemic blastomycosis. They reported that

the mode of onset in these cases was as follows:

In 50% of the cases the first symptoms were referable to the respiratory tract.

In 23% of the cases the earliest symptom was a subcutaneous nodule or abscess.

In 14% of the cases a skin lesion was noted first.

In 4% of the cases the primary lesion followed an injury of some kind.

The organs of predilection, according to these authors, were in the order of skin, subcutaneous tissue, lungs, bones and joints and, less commonly, the

central nervous system.

Involvement of the central nervous system by this organism is quite rare. Only 16 cases were found in the review by Martin and Smith. A case involving the meninges was reported by Friedman and Signorelli in 1946, and in their review of the literature fewer than 10 acceptable cases were found. Whitaker added four more cases from his review of the English literature in 1949. Kunkel et al. added five additional cases with meningeal involvement in 1954.

The treatment of systemic blastomycosis thus far has been generally unsuccessful and leaves much to be desired. In cases with meningeal involvement the prognosis is very poor. Martin and Smith <sup>16</sup> reported that 93% of the patients who died from systemic blastomycosis did so within a three-year period, and that the evaluation of any therapy for this disease before that period has elapsed should be interpreted with caution. In cases with proved meningitis the course has been uniformly fatal, and the duration of time from the onset of the meningitis to death has been very short.

In our review of the English literature plus personal communications, 2, 10, 21 we have been unable to find a case of proved blastomycosis meningitis treated

with amphotericin B.\*

We fully realize that it is much too early for adequate appraisal of the benefit of amphotericin B in this case. However, our results to date are most encouraging. Since this young man has now been followed for a period of three months and continues to be completely asymptomatic, with negative laboratory studies, perhaps amphotericin B will add new hope to patients afflicted with this entity.

## SUMMARY

A case of blastomycosis meningitis is reported in a 22 year old Negro male. The diagnosis was made by smear and culture of the spinal fluid. Treatment

<sup>\*</sup> Since preparing this case we have received word of a case of blastomycosis previously treated with amphotericin B who demonstrated a positive smear on spinal fluid for this organism.<sup>10</sup>

with amphotericin B was instituted with gradually increasing doses until a level of 75 mg. per infusion/day was attained. A total dosage of 2.65 gm. of the drug was administered to the patient over a 57-day period. The response was good, with gradual improvement in the spinal fluid and the clinical appearance of the patient. He has remained completely asymptomatic three months following discharge from the hospital, and is currently being followed in the Outpatient Clinic.

Although the post-treatment period is too short for any definitive conclusions, the patient's progress to date seems to warrant an optimistic view as to the success of this treatment.

#### ADDENDUM

Since writing this case for publication we have followed the patient for an additional four-month period. He was allowed to return to work in a car-wash station in March, 1959, and has not lost a day of employment from illness. He has remained completely asymptomatic, and has gained an additional 10 pounds in weight (140.5 to 151 pounds).

On June 9, 1959, a lumbar puncture was performed. The opening pressure was 120 mm. of water, the closing pressure, 110 mm. of water. The fluid was crystal clear in color, with a cell count of 3 lymphocytes. The total protein was 25 mg.%. Complement fixation done on this fluid was negative for blastomycosis as well as for coccidioidomycosis and histoplasmosis (antigen 1 and 2).

Blood studies done on the same date revealed: hemoglobin, 14.8 gm.; white blood count, 7,100, with a differential of 71 segs., 4 stabs, 20 lymphs, 4 monocytes and 1 eosinophil. The blood urea nitrogen was 16 mg.%, with a creatinine of 1.2 mg.%. Complement fixation on this serum was also negative for blastomycosis, coccidioidomycosis and histoplasmosis.

Nine months have now elapsed since the diagnosis of blastomycosis meningitis was made, and seven months since the patient was discharged from the hospital, and he has been on no specific medication. His continued good condition warrants further optimism for successful treatment.

#### ACKNOWLEDGMENT

The authors wish to express their thanks and appreciation to Dr. L. Palmer, Dr. R. Pappenfort and Dr. W. Kuzman for their kind assistance in the preparation of this paper.

#### SUMMARIO IN INTERLINGUA

Un masculo negre de 22 annos de etate esseva admittite al Hospital General del Contato San Diego le 10 de octobre 1959 con le diagnose de "blastomycosis cutanee", provate per biopsia ab un lesion del pelle ante le tempore del hospitalisation.

Al momento de su admission al hospital le patiente esseva describite como un ben-nutrite e ben-disveloppate masculo negre in stato de suffrentia moderate. Ille se plangeva de mal de capite e rigiditate del collo. Su signos vital esseva normal, excepte que su temperatura esseva 100,8 F. Su pelle esseva calide e sic, e le lesion supra le mandibulo dextere (ab ubi le specimen bioptic habeva essite prendite) esseva clarmente visibile. A parte le moderate rigiditate nuchal, le constatationes del examine physic esseva completemente intra le limites normal.

Le studios laboratorial esseva initialmente normal, sed studios de fixation de complemento in le sero esseva positive pro *Blastomyces dermatitides*. Frottis e cultura de liquido spinal esseva etiam positive pro *B. dermatitides*.

October 1959

Le tractamento esseva initiate con amphotericina B per lente infusion intravenose. Le dosage initial esseva 25 mg per die, solvite in 1.000 cm³ de aqua distillate. Le periodos de infusion continue esseva inter quatro e sex horas. Le dosage esseva augmentate secundo que le tolerantia pro le agente e le nivello del nitrogeno de urea sanguinee lo permitteva, usque le maximo de 75 mg per die (i.e. 1,25 mg per kg de peso corporee) esseva attingite. Post que un dosage total de 400 mg del droga habeva essite administrate, le previe gravamines del mal de capite e del rigiditate del collo habeva disparite. Le mesmo valeva pro le leve augmento de temperatura. A partir de iste tempore usque a su dimission ab le hospital, le patiente continuava meliorar se. Le 15 de decembre—i.e. post 66 dies al hospital e post haber recipite 2.650 mg (2,65 g) de amphotericina B in le curso de 57 dies—le patiente esseva dimittite ab le hospital e tenite sub observation al clinica pro patientes visitante.

Al tempore del presente reporto le patiente se trova sub observation posttherapeutic depost septe menses, i.e. novem menses ha passate depost le establimento del diagnose. Ille retornava a su empleo usual como lavator de automobiles in martio 1959 e non ha perdite un sol die de travalio a causa de maladia. Ille remane completemente asymptomatic. Studios de su sanguine e liquido spinal continua producer valores clarmente intra le limites del norma.

In nostre scrutinio del litteratura de lingua anglese nos non ha trovate un sol caso de confirmate meningitis blastomycetic que esseva tractate a bon successo. Iste caso pare justificar le conclusion optimista que un morbo, previemente quasi semper mortal, pote—in le futuro—esser tractate a bon successo.

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## CHLOROQUINE DIPHOSPHATE THERAPY IN **WEBER-CHRISTIAN SYNDROME\***

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RELAPSING febrile nodular nonsuppurative panniculitis (Weber-Christian syndrome) has been recognized with increased frequency. Little is known concerning its etiology. No specific therapy has been available.

Two cases of Weber-Christian syndrome are reported. The responses to chloroquine diphosphate were quite dramatic and gratifying.

## CASE REPORTS

Case 1. A white woman was first seen in May, 1947, when she was 40 years of age. For five years she had had recurrent attacks of painful, tender nodules in the calves of the legs and in the left thigh. Walking and standing gave rise to symptoms varying from discomfort to severe pain. On three previous occasions she had been admitted to hospitals with exacerbation of symptoms and elevation of temperature to 101° F. Twice she had had biopsies which were interpreted as a "nonspecific type of granulomatous inflammation consistent with nonspecific nodular panniculitis.'

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Previous therapeutic measures included (1) sulfonamides, (2) penicillin, and (3) salicylates, each without evident effect. During this fourth period of hospitalization she was given streptomycin, without improvement.

The physical examination disclosed a well developed and well nourished woman. The skin was warm. There were areas of induration over the lateral aspect of the left calf, the lateral aspect of the right calf, the lateral aspect of the right thigh, and the medial aspect of the left thigh. These areas measured from 1 to 6 cm. in diameter. The induration was accompanied by tenderness and increased local temperature. There was a scar on the lower inner left calf, the site of an earlier biopsy. On the medial aspect of the right calf there was an area, 7 cm. in diameter, of induration with a draining sinus, also the site of a biopsy performed one year previously. The remainder of the physical examination was entirely normal.

Urinalyses were entirely normal. Blood counts revealed a hemoglobin of 11.5 gm., an erythrocyte count of 3,510,000 per cubic millimeter, and a leukocyte count of 5,700 per cubic millimeter, with a differential count of 68% polymorphonuclears, 29% lymphocytes, 2% monocytes and 1% eosinophils. The electrocardiogram was within normal limits.

Oral temperatures during the period of hospitalization varied between 98° and 101° F.

This patient had been followed since 1947. The skin lesions persisted in varying severity. There were periods of several months when she was relatively comfortable, but at least several lesions were always present. There were repeated periods of exacerbations, with a low grade fever, malaise, new lesions, activation of old lesions, and reopening and drainage from the biopsy sites.

In the early autumn of 1950 the patient consulted a dermatologist because of a lesion on the left cheek which was variously diagnosed until September, 1952, when a biopsy was performed and interpreted as diagnostic of discoid lupus.

On September 15, 1954, because of the face lesion, the patient was given chloroquine diphosphate, 0.25 gm. twice daily for one week, and thereafter once daily. Three weeks later the face lesion was markedly improved. The patient excitedly reported marked improvement in the symptoms of the legs. Examination revealed fading of the face lesion and only slight inflammation and induration of the lesions in the calves of the legs.

After December, 1954, she was entirely free of all symptoms. Examinations at repeated intervals failed to disclose any tenderness, induration or nodules of the subcutaneous tissues. The lesion on the face disappeared entirely. Only a very small scar, the site of the biopsy, remains. Over each of the lower calves of the legs there were areas of deep pigmentation and scarring in the skin, without tenderness or induration. These were the sites of earlier recurrently draining lesions where biopsies had been performed.

Administration of chloroquine diphosphate was discontinued in August, 1955. The patient remained symptom-free until late in March, 1956, when there was sudden onset of pain and swelling in the left lower leg at the site of the biopsy scar, where a small area of increased local temperature and induration was demonstrated.

Chloroquine diphosphate therapy, 0.25 gm. twice a day, was immediately resumed. All pain, swelling and tenderness had disappeared 10 days later. The patient continued the chloroquine diphosphate, 0.25 gm. daily, through May, 1957. She has resumed full activities in the busy life of a housewife and mother. There have been no symptoms of intolerance to chloroquine diphosphate.

Case Summary: An adult female with a diagnosis of relapsing febrile nodular nonsuppurative panniculitis, confirmed by biopsy, had continued without complete remission for nine years. The fortuitous administration of chloroquine

diphosphate for a small discoid lupus lesion was followed by a dramatic remission in the panniculitis in 1954. A subsequent recurrence was arrested in 1956 by the reinstitution of chloroquine therapy.

Case 2. A 56 year old white woman was seen in February, 1956. She had had swelling of the arms and ankles for eight months. There had been nodules in the arm and about the ankles and lower legs. She had had a severe exacerbation six weeks before her consultation. This attack was associated with chills and fever to 100° F. Previous diagnoses had included erythema nodosum and rheumatic fever. She had received penicillin, without alteration in the clinical picture. Corticosteroids had been employed, with very dubious effect. She had been essentially confined to bed.

The past history included diagnoses of "rheumatic fever" at the ages of 14, 30, 37 and 40. She insisted that the current illness was identical with the illnesses at the ages of 37 and 40.

The physical examination disclosed moderate malnutrition. The lower legs showed redness, increased local temperature, and swelling below the midcalves. There were discrete subcutaneous nodules, 1½ cm. in diameter, over both lower legs, and smaller, similar nodules in the forearm. Several tender areas, without definite nodules, were palpated in the lateral abdominal walls. The pulse rate was 84. The blood pressure was 170/100 mm. Hg. There was a short, rough diastolic apical murmur. The heart was not enlarged on either physical or fluoroscopic examination. There was minimal sclerosis of both the peripheral and retinal arteries. There were no other pertinent physical findings.

The electrocardiogram was entirely within normal limits. The hemoglobin was 10.0 gm. The hematocrit was 35 mm. The leukocyte count was 6,900 per cubic millimeter.

A biopsy was not performed because of the possibility of a draining sinus occurring following the procedure.

Chloroquine diphosphate, 0.25 gm. twice a day, was started on February 15, 1956. Improvement was reported within 10 days. This improvement included loss of fever and a decrease in swelling and the fading of the nodules. The dosage of chloroquine diphosphate was reduced to 0.25 gm. daily. Improvement was quite marked and progressive in the course of the next two months. Only slight swelling and erythema in the left lower leg remained evident. The patient was able not only to carry on her light housework but also to engage in long daily walks. Her improvement has persisted. There is no edema of the lower legs. Deep pressure is mecessary to elicit any tenderness. Chloroquine diphosphate was discontinued after six months. She has returned to a fully active life in all respects. Reserpine, 0.25 mg. daily, was given for the hypertension.

Case Summary: A 56 year old woman with the clinical features of relapsing febrile nodular nonsuppurative panniculitis of eight months' duration is reported. She had had previous attacks which were interpreted as rheumatic fever but which may well have represented earlier episodes of panniculitis. The diagnosis was not confirmed histologically. She has had a dramatic remission with chloroquine diphosphate. Her status changed from confinement to her bed to full activity within a few weeks.

Comment: The etiology of this type of panniculitis has not been determined. Vitamin deficiency, chronic infection (Alderson and Way<sup>1</sup>) and hypersensitivity to various drugs have been suggested.

The histologic picture was well described by Bailey.<sup>2</sup> He referred to (1)

edema and necrosis of the subcutaneous fat, (2) a few multinucleated cells phagocytic for fat, (3) limited fibroblastic stimulation, (4) absence of epithelioid nodules, (5) infrequent, severe vascular change, and (6) primary involvement of an entire fat lobule,

The diagnosis of this disorder is difficult to establish. The clinical picture is described by its name. The characteristics of the Weber-Christian syndrome are adequately discussed by Bailey <sup>2</sup> as recurrent attacks of malaise and fever associated with painful subcutaneous nodules. Adult females are more frequently affected. The subcutaneous lesions in the panniculus under the skin are painful and tender, and are associated with inflammation of the overlying skin. The thighs, abdomen, lower legs and forearms are the usual sites of lesions. Subsequent to the attacks there may be atrophy of the fat tissue and depression of the skin at the site of the nodules. Persistent or recurrent draining sinuses at the site of biopsies have been characteristic.<sup>8</sup>

Therapeutic measures have been generally unsatisfactory. Hanson and Fowler suggested a high vitamin supplement. They had employed roentgen therapy, without benefit. Sulfonamides, antibiotics and corticosteroids and corticotropin have been used without demonstrable effect. Andrews, in his textbook, "Diseases of the Skin," states that "chloroquine diphosphate . . . in some instances has been beneficial." No further details are submitted.

#### SUMMARY

Two patients with relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian syndrome) had long-lasting remissions following the administration of chloroquine diphosphate.

#### SUMMARIO IN INTERLINGUA

Es reportate duo casos de recidive panniculitis nonsuppurative nodular febril (syndrome de Weber-Christian).

In le prime del duo patientes, le diagnose habeva previemente essite establite per biopsias in duo occasiones. Illa non habeva essite libere de manifestationes del morbo durante un periodo de novem annos. Biphosphato de chloroquina esseva prescribite a causa de un micre lesion diagnosticate como discoide lupus erythematose. Coincidentalmente un remission del panniculitis esseva observate. Le proxime recurrentia de panniculitis, duo annos plus tarde, respondeva de novo promptemente al reinstitution del therapia a biphosphato de chloroquina.

Le secunde patiente habeva habite le aspectos clinic de iste syndrome durante octo menses. In le passato, a plure occasiones in le curso de un numero de annos illa habeva habite maladias que nunc pareva esser interpretabile como episodios de morbo de Weber-Christian. In iste patiente, un remission dramatic del symptomas e signos sequeva le institution de un curso de biphosphato de chloroquina.

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## AMYLOIDOSIS SECONDARY TO CHRONIC **ULCERATIVE COLITIS\***

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Amyloidosis secondary to chronic ulcerative colitis is rare, only six cases having been reported in detail. The first was described by Moschcowitz 1 in 1936. Additional single cases were reported by Mallory 2 in 1947, Jensen et al.8 in 1950, and Frenkel and Groen in 1954. In 1955 Mandelbaum and Bryk 5 described two instances in a series of 108 cases of chronic ulcerative colitis autopsied at Mt. Sinai Hospital, New York, over a 20-year period. A few additional cases have also been briefly mentioned or tabulated.6, 7, 8 The following case is, we believe, the seventh to be reported in detail of amyloidosis associated with chronic ulcerative colitis.

#### CASE REPORT

A 26 year old white male patient was first admitted to Sinai Hospital on April 18, 1954, because of a fistula in ano, hemorrhoids and mild diarrhea of two months' duration. In recent weeks, discharges of blood and pus had appeared in the stools and he had gradually lost 10 pounds weight. Physical examination revealed a pale, chronically ill man, 5 feet 8 inches tall and weighing 111 pounds. The complete examination was essentially negative. Sigmoidoscopy disclosed thrombosed hemorrhoids, an anal fistula and a normal rectal mucosa. The stools were negative for pathogens and parasites. The hemoglobin was 11.7 gm.%. The leukocyte count was 4,900 cells per cubic millimeter of blood, and the differential count showed 1 stab, 61 segmented forms and 38 lymphocytes. The urinalysis was normal. The Mazzini serologic test for syphilis was negative. X-rays of the chest, the upper gastrointestinal tract, small bowel and colon were all normal. A hemorrhoidectomy and excision of a rectal abscess and anal fistula were performed. The operative site healed well, and the patient was discharged on April 30, 1954.

The patient improved initially but in the course of succeeding months the anal discharge, diarrhea and cramps reappeared. On August 14, 1954, the patient was hospitalized elsewhere and a right-sided colostomy was established to divert the fecal stream and a plastic repair performed on the anal canal. The surgeon reported

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that the mucosa of the colon appeared to be normal. Healing of the anal canal appeared to be satisfactory, and in December, 1954, the colostomy was closed.

Within a few months of the closure the discharge and diarrhea again returned, together with weight loss and general debility. Gross blood was not present in the stools. The spleen was palpable 2 cm. below the left costal margin. Tuberculosis was suspected despite a normal chest x-ray, and the microsections of tissues removed in April, 1954, were reviewed. These showed a moderate number of giant cells, with pale acidophilic cytoplasm and peripherally placed nuclei. A suggestion of epithelioid formation was noted. The possibility of tuberculosis could not be excluded.

The patient was hospitalized on the tuberculosis service of the Herman Kiefer Hospital, Detroit, on April 7, 1955. Chest x-rays, sputum culture and biopsy of an anal ulcer failed to establish a tuberculous etiology. He was treated for six months with streptomycin and isoniazid, without apparent improvement. In November, 1955, he was transferred to the University Hospital at Ann Arbor, where a barium enema disclosed chronic ulcerative colitis with pseudopolyposis. Sigmoidoscopy revealed changes compatible with chronic ulcerative colitis. Studies for tuberculosis were again negative. The urine at this time showed albumin and casts, and a diagnosis of chronic glomerulonephritis was made. He was discharged on November 19, 1955.

Shortly afterwards the albuminuria increased to 4 plus, numerous granular casts were found, and edema of the lower extremities and face was noted. Because of the presence of splenomegaly, albuminuria and edema, a diagnosis of amyloidosis secondary to chronic ulcerative colitis was suspected.

The patient was re-admitted to Sinai Hospital on December 31, 1955. Physical examination at this time revealed an emaciated male with mild pitting edema of the legs. The blood pressure was 90/60 mm. of Hg. A healed transverse surgical scar was present in the right upper quadrant of the abdomen. Sigmoidoscopy disclosed hyperemia and pinpoint bleeding after slight trauma. The urine contained 4 plus albumin, 20 to 30 white blood cells, 0 to 3 red blood cells per high power field, and numerous granular casts. The initial hemoglobin was 12.7 gm. The leukocyte count was 7,600 cells per cubic millimeter of blood, with a differential of 15 stabs, 47 segmented forms, 33 lymphocytes and 5 monocytes. The sedimentation time was 5 mm. in one hour (Westergren). The chest x-ray and the upper gastrointestinal and small bowel series were negative. The barium enema disclosed extensive chronic ulcerative colitis of the transverse and descending colon, with pseudopolyposis of the transverse colon. An intravenous pyelogram was normal. During hospitalization the specific gravity of the urine became fixed at around 1.010.

The blood urea nitrogen was 8.2 mg.%. The total protein was 3.9 gm., albumin 1.9 gm. and the globulin 2.0 gm. per 100 c.c. A phenolsulfonphthalein excretion test disclosed 30% excretion in 30 minutes and an additional 12.5% excretion of the dye at 60 minutes. The 24-hour urinary protein excretion was 6.0 gm. in a total urinary volume of 440 c.c. The total serum bilirubin was 0.4 mg.%; serum cholesterol, 250 mg.%; alkaline phosphatase, 7.5 Bodansky units. Cephalin cholesterol flocculation was negative in 48 hours. A bromsulfalein test disclosed 15% retention of the dye in 45 minutes at a dose of 5 mg. of dye per kilogram of body weight. Two L.E. cell preparations were negative. The serum sodium, potassium and chloride values were 140, 4.8 and 103 mEq./L., respectively. Serum calcium was 9.8 mg., and serum phosphorus, 4.4 mg.%. A Congo red test resulted in 67% removal of the dye from the blood at the end of one hour. At a later date a repeat test resulted in 92% removal of the dye. The sputum was negative for tubercle bacilli, and the tuberculin skin test was negative.

The patient was treated with a high caloric, low residue diet supplemented with

vitamins. Symptomatic treatment included the use of Kaopectate, paregoric and Donnatal. The patient ran an afebrile course, with an initial improvement and reduction of bowel movements to from three to six per 24 hours. The stools were negative for gross or occult blood, but because of the finding of cysts of Entameba histolytica he was given a 21-day course of chloroquine and Milibis. This resulted in no apparent improvement. Edema gradually became worse, involving all extremities and the face. The urine persistently showed 3 and 4 plus albumin. A mercurial diuretic was administered daily for three days, resulting in substantial reduction of the edema. The hemoglobin was 10 gm.% and the total serum protein 3.7 gm.%, with albumin of 2.0 gm. and globulin 1.7 gm.%. A renal biopsy (by Dr. T. Batchelor) revealed early evidence of amyloidosis. A liver biopsy disclosed no abnormality. Because of a low urinary 17-ketosteroid value (2 mg. in 24 hrs.) and the failure to increase after ACTH stimulation, the patient was given cortisone by mouth, the dose averaging 200 mg. daily.

On February 29, 1956, a colectomy was performed which included a resection of the terminal ileum and the colon as far as the midsigmoid. The surgical specimen, 85 cm. long, showed numerous petechial hemorrhages of the mucosa of the terminal ileum and extensive ulceration of the entire colon. The ulcers were disposed longitudinally and tended to be related to the tineal bands. The larger ulcers measured up to 8 cm. by 1.5 cm., and between them the mucosa was heaped up into pseudopolyp formations. Microscopically, the terminal ileum showed diffuse infiltration with eosinophils and lymphocytes in the subserosa. The appendix was mildly infiltrated and revealed a hyaline material which stained with Congo red. The cecum and colon were infiltrated with plasma cells and lymphocytes in the mucosa, with moderate fibrosis of the submucosa. The base of the ulcers was composed of a fibrinopurulent exudate with a deeper infiltration of lymphocytes, plasma cells and polymorphonuclear leukocytes. There were numerous crypt abscesses, and in some areas these had ruptured into the surrounding submucosa. The small arteries of the adventitia showed intimal hyalinization. There was no amyloid deposition in the colon. Giant cells of the Langhans type were scattered throughout the sections but in no particular relation to the lesions. No tubercle formation was present, and stains for acid-fast bacilli were negative. The anatomic diagnosis was chronic ulcerative colitis in the subacute phase, and amyloidosis of the appendix.

Postoperatively the patient appeared to make excellent progress. He was out of bed on the first postoperative day and the cortisone was gradually reduced. The ileostomy functioned normally. However, on the fifth postoperative day, while

ambulatory, the patient suddenly collapsed and died.

Postmortem Examination: The body was that of a moderately well nourished white male, appearing somewhat younger than the stated age. The lower abdomen revealed a recent right paramedian surgical incision, through which the sigmoid was brought up through its lower portion as a mucous fistula. An ileostomy stoma was present just to the left and below the umbilicus, and a healed transverse incision scar was present in the right upper abdomen. There was pitting edema of the ankles and the skin was pale, with cyanosis of the head, neck and upper chest. The subcutaneous fat was scanty. The peritoneal cavity contained no free fluid, and the linings were not unusual. The pericardium was normal. The pulmonary artery, its main branches and the pulmonary conus were completely occluded by a large antemortem thrombus. It extended into the right secondary pulmonary artery. The heart weighed 215 gm. but showed no abnormality of the valves or its walls. The coronary arteries, the aorta and the medium sized arteries of the body showed no atherosclerosis. The portal and pelvic veins and the venae cavae were free of thrombi and emboli. However, the left profunda femoris vein was occluded by a firmly adherent thrombus. The lungs showed no evidence of active pulmonary tuber-

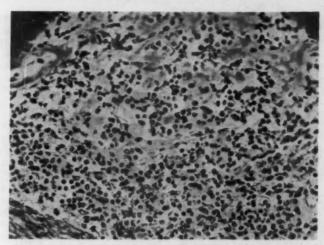


Fig. 1. Spleen at post mortem, showing amyloid deposit in the upper third, with well preserved red pulp and trabeculum in the lower portion. Hematin, phloxine and saffron.  $\times$  135.

culosis, but there was a 1 cm. obsolete fibrocaseous tubercle in the right apex. The gastrointestinal tract showed slight focal hyperemia throughout the small bowel mucosa, while the lower sigmoid and rectum remaining in situ showed no gross lesions. The liver weighed 2,125 gm. It was homogeneously yellow-brown, firm, somewhat translucent, and without focal lesions. The kidneys weighed 145 gm. (right) and 155 gm. (left). Their architecture was intact but the organs were diffusely pale. The spleen weighed 350 gm. It was covered by a smooth, glistening

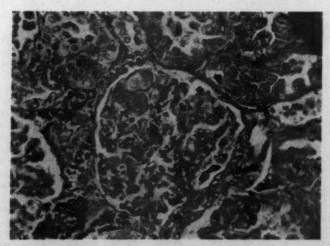


Fig. 2. Kidney from autopsy specimen, showing amyloid deposit in the glomeruli, particularly upper left tuft. Congo red stain positive. The picture was similar in the needle biopsy previously obtained. Hematin, phloxine and saffron.  $\times$  300.

capsule and was moderately firm, with a sharp edge. The parenchyma scraped with moderate ease, appeared slightly pale and presented no focal lesions. The gall-bladder, pancreas, thyroid, adrenals, testes, pituitary, abdominal lymph nodes, bone marrow and brain (1,725 gm.) were grossly normal.

Microscopic Examination: The lungs showed minute areas of atelectasis, and several large veins were occluded by a thrombus of recent origin. The spleen showed large areas of replacement by hyaline material of the parenchyma, particularly within the malpighian corpuscles (figure 1). This material stained with Congo red in frozen sections and was present also in the vessel walls. The cortex of the adrenal glands revealed moderate replacement by the same material. The kidneys also showed marked deposition of amyloid in the glomeruli beneath the basement membranes of the capillaries (figure 2) and some of the tubules. Sections of the liver exhibited marked deposition of the hyaline material beneath the endothelium of the sinusoids, with compression of the liver cords. The residual large intestine showed only a few zones of submucosal thickening, but no lesions of the mucosa or the remainder of the wall. There was no amyloidosis in the wall of the colon. The small bowel showed only slight focal hyperemia. Sections of the heart, pituitary, thyroid, pancreas, testes, prostate and bone marrow showed no significant microscopic lesions.

Anatomic Diagnosis: Chronic ulcerative colitis; edema of legs; phlebothrombosis of left femoral vein; massive embolism of pulmonary artery; amyloidosis of liver, spleen and adrenal glands.

#### DISCUSSION

In an intestinal disease such as chronic ulcerative colitis, in which chronic inflammation and suppuration are essential features, it is remarkable that secondary amyloidosis has been reported so rarely. Even in instances of ulcerative colitis in which perirectal fistulas and abscesses are conspicuously present, amyloidosis has been rare. Mandelbaum and Bryk,<sup>5</sup> for example, found six cases of ulcerative colitis where perirectal infection and fistulas were present; none of them showed amyloidosis. However, one of the two cases of amyloidosis associated with ulcerative colitis which they reported in detail showed perirectal infection. Jensen et al.<sup>8</sup> stressed the importance of perirectal infection accompanying ulcerative colitis in the pathogenesis of amyloidosis. Our own case is in accord with this concept.

The case of secondary amyloidosis herein reported is unusual because of the brief duration of the antecedent chronic ulcerative colitis, a period of probably less than two years. The six patients previously reported in the literature had symptoms of ulcerative colitis for five years in three instances, and for from 10 to 20 years in the remaining three. It is apparent that long duration of ulcerative colitis is not a prerequisite for the development of amyloidosis.

When albuminuria or a nephrotic syndrome appears in a patient suffering from chronic ulcerative colitis, the possibility of secondary amyloidosis should be entertained, especially after the acute toxic or febrile phase of ulcerative colitis has subsided. In the acute febrile stage of the primary disease the albuminuria may be due to the nonspecific glomerulitis characterized by endothelial proliferation, described by Jensen, Baggenstoss and Bargen.<sup>9</sup> In their series the lesion occurred in 42 of 60 cases of ulcerative colitis. The amount of albumin varied from day to day, and was apt to diminish when the colitis subsided. In renal amyloidosis, by contrast, the albuminuria is more constant and shows little daily fluctuation. A large, firm liver and splenomegaly in a

patient with ulcerative colitis also suggest amyloidosis. A highly positive Congo red test and needle biopsy of the liver and kidney may provide confirmation of this diagnosis. The suspected diagnosis was confirmed in our patient by needle biopsy of the kidney.

Amyloid nephrosis may be difficult to distinguish from chronic glomerulonephritis, a rare complication of chronic ulcerative colitis. In this distinction the absence of high blood pressure in amyloid nephrosis may be important. Renal biopsy is particularly helpful in establishing the correct diagnosis.

Despite the presence of amyloidosis, a total colectomy was planned for this patient in the hope that removal of the focus of suppuration might lead to regression of the amyloid deposits. This has been shown to occur in tuberculosis and other chronic suppurative diseases when the primary focus of inflammation has undergone regression.<sup>1, 5, 10, 11</sup> Rosenblatt,<sup>10</sup> for instance, reports the recovery of a patient with generalized amyloidosis including a nephrotic syndrome in whom the disease was secondary to extensive pulmonary tuberculosis. In the six previously reported instances of amyloidosis associated with chronic ulcerative colitis, total colectomies were not performed. In the present case the unfortunate death of the patient due to postoperative pulmonary embolism prevented clinical observation of the course of amyloidosis following the removal of the diseased colon.

#### CONCLUSION

Amyloid infiltration secondary to chronic ulcerative colitis is a rare occurrence. The case herein described is the seventh to be reported in detail. Interesting features included the presence of a chronic perianal fistula which preceded clinical and roentgenologic manifestation of ulcerative colitis, the short duration of the primary disease (less than two years), and the use of needle biopsy of the kidney to establish the diagnosis.

#### SUMMARIO IN INTERLINGUA

Amyloidosis secundari a chronic colitis ulcerative es rar. Solmente sex casos se trova reportate in detalio in le litteratura. Le presente caso es illo de un masculo de racia blanc de 26 annos de etate in qui le colitis ulcerative chronic se declarava per leve grados de diarrhea, hemorrhoides, e un fistula in ano que secerneva sanguine e pus. Le excision chirurgic del fistula e del hemorrhoides resultava in solmente un alleviation temporari, e post un certe tempore un colostomia dextero-lateral esseva establite pro promover le restauration. Post le clausion del colostomia quatro menses plus tarde, le diarrhea e le effluxo rectal recurreva, e le possibilitate de un etiologia tuberculotic esseva prendite in consideration. Mucobacterium tuberculosis esseva demonstrate a nulle tempore, e sex menses de therapia con streptomycina e isoniazido resultava in nulle melioration. A iste tempore-circa 20 menses post le declaration del morbo-studios radiologic revelava chronic colitis ulcerative con pseudopolyposis. Al tempore del hospitalisation terminal de iste patiente, le constatation de allargamento del splen, de albuminuria, e de edema, supportava le suspicion de nephrosis amyloide, secundari a chronic colitis ulcerative. Isto esseva confirmate per biopsia renal a agulia. Duo annos post le prime declaration de symptomas, un colectomia subtotal esseva effectuate, con le plano de extirpar le sigmoide inferior e le recto in un secunde phase del operation. In despecto del apparentia de un excellente progresso, le patiente collabeva e moriva le quinte die post le operation. A ille tempore le patiente esseva jam ambulatori. Un examine

del specimen chirurgic e le necropsia revelava chronic nonspecific colitis ulcerative, amyloidosis del appendice, del hepate, del splen, e del glandulas suprarenal, phlebothrombosis del vena sinistro-femoral, e un embolismo massive del arteria pulmonar.

In despecto del inflammation e suppuration que es characteristicas prominente de chronic colitis ulcerative, amyloidosis secundari es rarmente associate con illo. Aspectos interessante del presente caso es le chronic fistula in ano que precedeva le manifestationes clinic e roentgenologic del chronic colitis ulcerative, le curte duration del morbo primari (minus que duo annos), e le uso de biopsia renal a agulia pro establir le diagnose de amyloidosis renal. Le diagnose differential de albuminaria in patientes con chronic colitis ulcerative debe prender in consideration amyloidosis secundari, glomerulitis nonspecific, e glomerulonephritis chronic. Colectomia total esseva planate pro le patiente del presente reporto, sed le supervenientia de morte in consequentia de embolismo pulmonar postoperatori preveniva le observation clinic del expectate regression del amyloidosis secundari.

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## SCLEROMALACIA PERFORANS AS A COMPLICATION OF RHEUMATOID ARTHRITIS: REPORT OF A CASE AND OBSERVATIONS CONCERNING THERAPY \*

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This relatively rare complication of rheumatoid arthritis was first reported by van der Hoeve in a talk given before the Royal Dutch Ophthalmological

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Society in 1930 which was subsequently published in 1931. After this report there were several other case reports, and in 1938 Verhoeff and King 2 analyzed 14 previously reported cases, and added another to the literature. In 1952 Anderson and Margolis 8 reviewed the literature and reported that there were approximately 30 cases of scleral disease, either similar or related in varying degrees to this condition. However, not all of these were associated with rheumatoid arthritis. Some were probably different disease entities. They state that if only those cases with scleral involvement as an accompaniment or secondary to rheumatoid arthritis are considered, less than 20 cases can be accepted. In 1952 Goar a reported two cases, both undiagnosed until after enucleation. Mathias 5 added an additional case in 1955. He reported that the joint involvement was severe. Ocular involvement began while the patient was receiving adrenal steroids, and further steroid therapy did not seem to influence the course of the disease. In 1956 Margyard 6 reported two sisters with rheumatoid arthritis and scleromalacia perforans; in both therapy was ineffective, and enucleation seemed inevitable.

A survey of the literature seems to support the premise that scleromalacia perforans is a complication of rheumatoid arthritis and actually represents rheumatoid involvement of the sclera. The small number of case reports suggests that this is a rare complication. Involvement is often bilateral, and blindness frequently results.

#### CASE REPORT

A 32 year old white female was first seen by one of us (G. T. W.) on October 17, 1955. She had typical severe rheumatoid arthritis of five years' duration. Multiple joint effusions were present, and there were moderately advanced joint deformities involving more severely the proximal interphalangeal and metacarpophalangeal joints, as well as many other peripheral joints. A large granulating ulcer was present over the right lateral malleolus. This had resulted from minimal trauma, and healed satisfactorily after a split-thickness skin graft was applied. The patient was started on a therapeutic program including rest, exercises, heat, salicylates and prednisone, 20 mg. daily. However, she had been on steroid therapy for several years prior to our initial treatment.

There was evidence of continuing rheumatoid activity, manifested by joint effusions, rheumatoid nodules on the dorsum of the hands, and progressive joint destruction. On November 25, 1955, the patient reported that for several days there had been fairly severe pain in both eyes, and some redness of the conjunctiva. On examination the visual acuity was 20:20. The bulbar and palpebral conjunctivae were injected. The lacrimal apparatus was patent, and the extraocular muscles balanced. The finger tension was soft, and the pupils were equal and reacted well to light and accommodation. The optical media were clear, and the fundi were normal. Therapy was begun with 2½% hydrocortisone eyedrops, but there was no improvement, and two weeks later a conjunctival ulceration was noted involving the left eye near the limbus. Twenty-five one hundredths of a cubic centimeter of 0.5% hydrocortisone was then injected subconjunctivally, but there was no response, and 10 days later the ulcer was found to be larger. In addition, a purulent conjunctivitis was present. The latter cleared with the use of topical antibiotics, compresses and supportive therapy. The ulceration, however, remained. Because of the possibility that the prednisone was inhibiting healing, this was discontinued for a period of several weeks. At first a slight improvement was noted, but then ocular pain became more severe, and there was a marked flare-up in the activity in the joints.



Fig. 1. Right eye, showing exposed choroid above cornea, mucopurulent discharge.

Steroid therapy was re-instituted, using hydrocortisone. The initial dosage of 120 mg. daily was gradually reduced to 60 mg. daily. The patient subsequently developed two conjunctival ulcers on the right eye, one above and the other below the limbus. The scleral ulcerations gradually grew larger in spite of the local and systemic therapy, and finally the left sclera perforated. This was repaired three days later by mobilizing and plicating Tenon's capsule above and below this area. Visual acuity in the right eye was 20:40 and in the left, 20:100. Progressive ocular destruction continued, with the development of a much larger ulcerated area in the right conjunctiva above the limbus. Scleral dehiscence resulted, and the black choroid could



Fig. 2. Left eye, showing repaired chorioretinal rupture lateral to cornea.

be seen bulging through this area (figures 1 and 2). The vision on the right decreased to 20:100, and on the left only slight light perception persisted. To cover this large area, on December 21, 1956, a scleral transplant was done. Later a conjunctival bridge graft was necessary to cover the transplanted sclera. The relentless course of the disease continued, and in August, 1957, the right cornea perforated and the anterior chamber collapsed. Then, in October, 1957, the left cornea perforated. Since then the patient has had only slight light perception, and has continued to have fairly severe ocular pain.

In the two and one-half years that we have observed this patient her rheumatoid arthritis has remained active and fairly severe, with progressive joint destruction. In addition to the measures previously outlined, she was given 1,200 mg, of Myochrysine,

without effect on the activity of the joint or ocular involvement.

#### DISCUSSION

Scleromalacia perforans seems well established as a rare complication of rheumatoid arthritis. Talkov  $^{\tau}$  in 1951 reported that serial pathologic studies of the scleral nodules in his patient were identical with those of rheumatoid nodules elsewhere in the body. Fortunately, this ocular complication is extremely rare. In general it is more frequent in patients in the older age group, and in a partial survey of the literature we found no patients younger than the one we have reported, in whom ocular involvement began at the age of 32 years. The previous reports have pointed out the limited response to therapy and the poor prognosis. The process usually becomes bilateral and blindness frequently results. In our case therapy with local and systemic steroids, gold salts and salicylates was ineffective. The course of the eye disease was steadily downward, and did not directly parallel the joint changes. In those cases in whom the severity of the arthritis has been noted, it seems that scleromalacia perforans is more frequent in those with very severe rheumatoid arthritis.

Therapy for the ocular involvement will remain empiric and symptomatic until a specific treatment for rheumatoid arthritis is discovered. The adrenal steroids locally and parenterally do not seem to be helpful. While there is not a definite parallel between the severity of the joint disease and the occurrence of scleromalacia perforans, it is more frequent in patients with severe arthritis and with marked systemic symptoms. It seems likely that if the activity of this systemic disease could be reduced the ocular involvement would also decrease. Aside from the steroids, at present only the gold salts and possibly chloroquine have this effect. Because of these considerations, their use should probably be more seriously considered when scleromalacia perforans occurs as a complication of rheumatoid arthritis. Unfortunately, up to the present it has often proved impossible to allay the activity of the disease, and blindness has frequently resulted.

#### SUMMARY

 The course of a 32 year old patient with scleromalacia perforans as a complication of rheumatoid arthritis is presented.

2. The response to therapy was poor, and the ocular involvement progressed to blindness.

3. Local and systemic treatment is discussed.

#### SUMMARIO IN INTERLINGUA

Es reportate le caso de un femina de racia blanc de 32 annos de etate con scleromalacia perforante como complication de arthritis rheumatoide. Illa habeva typic arthritis rheumatoide de forma sever depost cinque annos quando le symptomas ocular esseva primo notate. Initialmente illa habeva satis sever dolores in ambe oculos. Le conjunctiva monstrava un certe grado de rubor. Postea, ulcerationes conjunctival se disveloppava bilateralmente. În despecto de therapia con steroides local e systemic, le morbo progredeva. Le patiente disveloppava perforationes in ambe oculos e deveniva cec. In le curso del duo annos e medie durante le quales nos ha observate iste patiente, le arthritis rheumatoide ha remanite active e sever. Il ha occurrite un progressive destruction articular.

Un revista del litteratura ha producite circa 20 casos de scleromalacia perforante como complication de arthritis rheumatoide. In general, le condition prefere patientes de etates plus avantiate. Nos ha trovate nulle caso in que le patiente esseva plus juvene que le nostre, qui habeva 32 annos quando le affection ocular se initiava. Previe reportos signala le magre responsa al therapia e le pauco favorabile prognose. In nostre caso, therapia con steroides local e systemic, sales de auro, e salicylatos esseva inefficace. In essentia le morbo representa nodulos rheumatoide in le sclera. Illo pote esser unilateral al initio, sed usualmente le secunde oculo va etiam esser afficite. Le prognose es uniformemente pauco favorabile, e cecitate es un resultato frequente.

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## PRIMARY CLOSTRIDIAL PNEUMONIA \*

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Although William Welch in his early descriptions of human infection with clostridial organisms records two cases of lung infections (exact type un-

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described), there has been a paucity of similar reports since that time. Clostridium perfringens infection occurring in the chest cavity following penetrating wounds of the thorax is well known. In the absence of direct injury to the chest, however, primary clostridial pneumonia or a parenchymal infection secondary to hematogenous dissemination from a distant locus is quite rare. The following case report deals with primary pneumonia due to C. perfringens (Clostridium welchii).



Fig. 1. X-ray taken the night of admission, showing large right pleural effusion.

#### CASE REPORT

A 45 year old white housewife was admitted to the medical service of Presbyterian Hospital on November 18, 1957, with the complaints of dyspnea and ankle swelling of from seven to 10 days' duration. Family and social histories were not contributory, and personal history revealed only a minimal intake of alcohol. Her past health had always been excellent. The present illness had begun three to four weeks prior to admission, when she had experienced three or four days of headache, backache and a "feverish feeling," without cough, nausea, vomiting, diarrhea or chills. The original symptoms subsided in 72 hours without treatment, but she continued to feel weak, tired and breathless on slight exertion. Ten days before admission she noted severe dyspnea on climbing two flights of stairs, and approxi-

mately one week later she complained of swelling of her feet and ankles as well as dyspnea. Within 48 hours the swelling involved her entire lower extremities, and she therefore sought admission.

Physical examination revealed a critically ill white woman with obvious jaundice, cyanosis and tachypnea. Pulse, 150 per minute; respirations, 30 per minute and shallow; blood pressure, 180/110 mm. of Hg in both arms; temperature, 102.6° F. The sclerae were icteric, but no spider angiomata or other skin lesions were noted.



Fig. 2. X-ray taken after removal of 500 c.c. of bloody fluid. Film is overpenetrated to show air collection in right upper quadrant, suggesting loops of bowel.

Neck veins were distended and filled from below. Examination of the lungs revealed dullness over the lower half of the right lung posteriorly, with markedly diminished breath and voice sounds over the right lower lobe. No signs of consolidation were elicited, and the left lung was essentially clear. The original chest x-ray (figure 1) showed evidence of a large right pleural effusion. The left heart border was found at the anterior axillary line in the sixth intercostal space, but no rub, gallop or significant murmurs were audible. The electrocardiogram showed a sinus tachycardia with evidence of myocardial disease. The liver and spleen were

not palpable, and bowel sounds were hypoactive. There was massive pitting edema of the lower extremities and presacral region and abdominal wall, but no periorbital edema. The remainder of the physical examination was within normal limits.

Laboratory data were as follows: erythrocyte sedimentation rate, 14 mm.; hematocrit, 50%; hemoglobin, 15.5 gm.; white blood cell count, 20,600, with 90% polymorphonuclears and a marked shift to the left. Urinalysis showed only 2 plus proteinuria. Serum bilirubin was 14.4 mg.% (all direct); cephalin flocculation, 2 plus; thymol turbidity, 2 plus; prothrombin time, 26 sec., alkaline phosphatase, 2.6 Bessie-Lowry units (normal, 0.8 to 2.3 units). Serum electrophoresis showed albumin reduced to 1.2 gm.%, with total protein of 4.7 gm.%.

The patient was digitalized for her obvious congestive heart failure, and was given Mercuhydrin. A thoracentesis was performed in an attempt to alleviate her extreme respiratory distress. Five hundred cubic centimeters of bloody pleural fluid were obtained and were reported to show gram-negative bacilli and a very few white

cells. Ziehl-Neelsen stain of the fluid showed no acid-fast organisms.

Chest x-ray following thoracentesis (figure 2) showed a decrease in the size of the pleural effusion but also demonstrated an abnormal gas shadow in the right upper quadrant suggestive of free air beneath the diaphragm. The x-ray findings were interpreted as evidence of either interposition of bowel between diaphragm and liver or possibly herniation of bowel into the right pleural cavity through the diaphragm. As studies were being undertaken to delineate the portion of the bowel affected, the patient's respirations suddenly became very labored and ceased while a tracheotomy was being performed. She had been in the hospital less than 30 hours.

Although the results were not obtained before death, five of six antemortem blood

cultures and the pleural fluid culture grew C. perfringens.

At postmortem examination the deep icterus and marked pitting edema of the lower extremities were noted. The right diaphragm was intact, and all abdominal organs were in their normal positions. There was extensive necrotizing pneumonia of the right middle and lower lobes. The entire lower portion of the right pleural space was obliterated by a nest of air pockets separated from each other by thin septa. Eight to 10 of these pockets were of sufficient size that air could be heard escaping as the septa were broken. An extremely foul smelling yellow-green fluid was also present in the larger pockets. Other outstanding findings were moderate left ventricular hypertrophy and marked hepatomegaly with extensive centrolobular necrosis. There was no evidence of instrumentation of the cervix or uterus, nor was any obvious portal of entry or other locus of gangrene found.

Postmortem cultures of the lung and pleural fluid also grew C. perfringens.

#### DISCUSSION

In the above case it seems obvious that we are dealing with primary C. perfringens pneumonia and pulmonary abscess formation. In the absence of any history or findings suggestive of trauma or aspiration (there had been no vomiting or periods of unconsciousness prior to admission), and with no other locus of infection to be noted, a primary C. perfringens pneumonia appears to be the only reasonable diagnosis. The gram-negative rods that were originally reported from the thoracentesis fluid were, on reëxamination, almost certainly Clostridia. The isolation of this organism from the blood and pleural fluid as well as from culture of the postmortem lung amply confirms this. The centrolobular liver necrosis, which is reflected in the markedly abnormal liver function studies, was probably a result of a severe "toxic" state. Actual bacteria could not be detected in the liver. The mechanism for the accumulation of

edema in this patient is not fully apparent, although the marked hypoalbuminemia undoubtedly played a role.

An interesting aspect of this case is the chest x-ray taken after the thoracentesis (figure 2). The obvious air pockets high in the right upper quadrant of the abdomen presumably resulted from gas production by the organism in the lung and pleural space. However, so closely did they mimic loops of bowel, either immediately subdiaphragmatic or herniated into the right chest, that surgery was considered mandatory and emergency preparations for operation were underway when the patient died.

Review of the literature reveals very few cases of well documented C. perfringens pneumonia. Jacox in 1951 \* reported a 30 year old woman admitted with six days of cough, sputum and fever, with an x-ray picture that showed the development of an abscess cavity in the right lung over a three-day period. C. perfringens was cultured from fluid obtained at open drainage. Six weeks before admission the patient had noted a reddened, tender area over the right lateral malleolus, and this may have been a site of entry for the organism, with subsequent hematogenous spread to the lung. A primary pneumonia, however, seems more likely. Following drainage, the patient did well on antibiotics and antiserum. In 1952 O'Donnell \* reported the case of a 52 year old woman who developed pneumonia a few days after a subtotal gastrectomy for duodenal ulcer. Some vomiting apparently had occurred preoperatively, and aspiration may have played some role in initiating the process. C. perfringens was cultured from the thoracentesis fluid as well as from the nose, and the patient recovered after prolonged treatment with penicillin and antiserum. Aspiration almost certainly played a role in a case reported by Glaser 5 of a 41 year old man who developed a lung abscess one week after sustaining the loss of a number of carious teeth following trauma. In this case, C. perfringens was only one organism in a mixed flora. A single case of C. perfringens pneumonia without details is mentioned in a series from The Mayo Clinic by Ghormley.

C. perfringens has been cultured from a variety of human sources. It is a well recognized inhabitant of the vagina, and has also been reported in the gastrointestinal tract, in the mouth about carious teeth, in peritonsillar abscesses and in the postmortem liver. In addition, in the preantibiotic era it was frequently found in the sputum of patients with open cavitary tuberculosis. It is therefore somewhat surprising that it is not a more common etiologic agent of lung abscesses, many of which are essentially anaerobic. A partial explanation for this is undoubtedly a failure to search with appropriate cultural methods, but, in addition, there are probably still poorly understood inherent properties of the organism which prevent its propagation under such conditions.

#### SUMMARY

- 1. A case of a primary pneumonia with lung abscess formation due to C. perfringens is presented.
- 2. Review of the literature reveals only two other reasonably well documented cases of primary pneumonia due to this organism.

#### SUMMARIO IN INTERLINGUA

In despecto del facto que William Welch publicava su description del infection clostridial del pulmon jam in 1941, le annos depost ille tempore es distinguite per un marcate paucitate de reportos de casos de ille condition. Le presente reporto concerne un caso de primari pneumonia a Clostridium perfringens, occurrente in un previemente san subjecto feminin de racia blanc de 45 annos de etate. Illa entrava in le Hospital Presbyterian a New York con un historia de tres septimanas de dorsalgia, malaise, dyspnea post effortio, e edema del cavilias. Le examine physic revelava que le patiente esseva acutemente malade, cyanotic, febril, e icterie, con evidentia de congestive disfallimento cardiac e effusion dextero-pleural. Pertinente constatationes laboratorial es: Numeration leucocytic-20.000, con 90% polymorphonucleares; bilirubina-14,4 mg pro cento; albumina del sero-1,4 g pro cento; e flocculation cephalinic e turbiditate thymolic-2+. Le patiente moriva subitemente 30 horas post su admission al hospital, ante que un diagnose definite poteva esser establite. Le examine necroptic revelava sever pneumonia necrotisante in le lobo dexteroinferior. Multiple cavitates abscessal esseva presente. Illos esseva plenate de gas e liquido de un odor putride. Sever necrosis centrolobulo-hepatic esseva le sol altere constatation remarcabile. Nulle porta de entrata e nulle evidentia de instrumentation gynecologic esseva trovate. Culturas de sanguine (effectuate cinque vices), de liquido pleural, e specimens necroptic de histos pulmonar produceva omnes crescentias de C. perfringens, de maniera que le diagnose de pneumonia clostridial e septicemia poteva esser establite.

Le roentgenogramma thoracic esseva de interesse special. Illo monstrava multiple superficies de aere e liquido in le thorace dextere. Istos habeva le apparentia de ansas intestinal. Iste aspecto deceptori esseva causate sin dubita per le abscessos a tenue parietes que esseva locate in le lobo dextero-inferior e per le abundante formation de gas per le anaerobie bacillo de Welch.

Un meticulose scrutinio del litteratura revela solmente duo ben-documentate casos de primari pneumonia clostridial sin apparente porta de entrata o lesion precedente.

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# MYOCARDIAL SARCOID, COMPLETE HEART BLOCK AND AORTIC STENOSIS \* †

By ROBERT E. BOTTI, M.D., and FRANK E. YOUNG, M.D., Cleveland, Ohio

COMPLETE heart block in a young adult may pose a difficult diagnostic and therapeutic problem. The subject of this case report illustrates these difficulties and is of unusual interest because of the autopsy finding of myocardial sarcoid in addition to the clinically apparent rheumatic heart disease with aortic stenosis.

## CASE REPORT

A 32 year old white female was admitted to University Hospitals of Cleveland on August 8, 1957, having had fainting spells of six months' duration.

This patient had been asymptomatic until six months before admission, when she suddenly became unconscious for a few seconds while playing cards. She awoke and felt dizzy and dyspneic, but immediately lost consciousness again for an equally brief period. These episodes were attributed to influenza and were treated symptomatically. Following this there were frequent episodes of lightheadedness, dyspnea, precordial tightness, and slow, hard pounding of the heart. Eight days before admission the patient fainted while washing dishes, and electrocardiographic evidence of complete atrioventricular dissociation was found. She was admitted to another hospital, and when treatment with Isuprel and atropine was unsuccessful she was transferred to University Hospitals.

There was no past history of rheumatic fever, cardiac murmurs, diphtheria or other infectious disease. The patient had been born in Ohio and had lived there all her life.

Physical examination revealed a pale, well nourished, apprehensive but alert young female in no distress. Her temperature was 38.2° C. rectally; blood pressure, 106/44 mm. of Hg; respiration, 24; pulse, 42. The abnormal findings were limited to the heart and abdomen. The apex beat was forceful and was located just outside the midclavicular line in the left fifth intercostal space. No thrills were present. There was a moderately loud, harsh, blowing systolic murmur, heard best in the aortic area and the third left intercostal space next to the sternum. This was transmitted to the neck and back. A soft, blowing, decrescendo aortic diastolic murmur was also heard. The second aortic sound was absent. No apical murmurs were heard. No friction rubs were present. The rhythm was regular. The liver edge was slightly tender and was palpable 4 cm. below the right costal margin. There was no splenomegaly, venous distention, cyanosis, ascites, peripheral edema, splinter hemorrhages or subcutaneous nodules. The lungs were clear, and there was no lymphadenopathy.

Urinalysis was normal. The hematocrit was 41%; white blood cell count, 13,000; sedimentation rate (Wintrobe), 9 mm./hr. Platelets were adequate. Other laboratory data included a creatinine of 1.3 mg.; albumin, 3.7 gm.; globulin, 1.8 gm.; cholesterol, 122 mg.; transaminase, 42; C-reactive protein, 3 plus; repeated the

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following day, 1 plus; prothrombin time, 52%; A.S.O. titer, 100; serologic test for syphilis, negative; stool guaiac, negative; blood and throat cultures, negative.

Venous pressure was 210 mm. saline, and the arm-to-tongue circulation time was 34 seconds. Portable anteroposterior x-ray showed probable cardiac enlargement and lung fields grossly free of disease (figure 1).

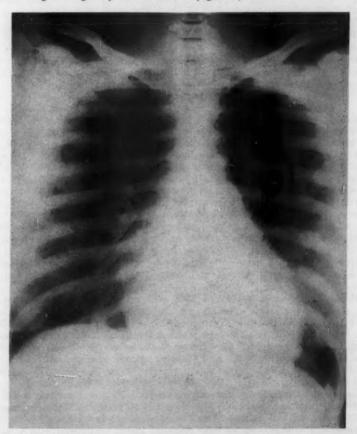


Fig. 1. A-P portable chest roentgenogram, demonstrating cardiac enlargement and absence of pulmonary findings.

Hospital Course: The electrocardiogram on admission showed complete atrioventricular dissociation, with an atrial rate of 118 and an idioventricular rate of 46 (figure 2). The initial impression was rheumatic heart disease, aortic stenosis and mild congestive heart failure.

Atropine and sublingual Isuprel were started and, because of the heart failure, slow digitalization with digitoxin was begun. On the afternoon of August 16, asystole occurred and the patient became cyanotic and unconscious. Ventricular flutter was noted, but soon the rhythm reverted to regular sinus rhythm at a rate of 72 following intravenous Pronestyl. After a few minutes complete dissociation recurred. Isuprel and digitoxin were stopped because of an increasing number of

ventricular premature beats. Hydrocortisone, 100 mg., was given by intravenous drip over an eight-hour period.

Beginning at 1 a.m. on August 18 the patient experienced periods of asystole every 30 to 60 minutes. At first intravenous Isuprel was used, but this was discontinued because of the rapid appearance of runs of ventricular premature beats. The asystolic periods subsided spontaneously or with pounding on the precordium. Intravenous molar sodium lactate was tried unsuccessfully and precipitated the onset of moderate left ventricular failure. At this point it was felt that emergency aortic valvulotomy should be attempted in an effort to increase coronary flow to the myocardium and conducting system.

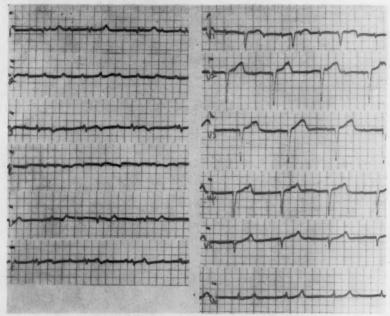


Fig. 2. Electrocardiogram showing complete A-V block with idioventricular rate of 46.

On the afternoon of August 18, Dr. Claude Beck performed an aortic valvulotomy through a sleeve in the aorta, and also a left vagotomy below the left recurrent laryngeal nerve. During the thoracotomy before the valvulotomy, ventricular flutter occurred, followed by ventricular fibrillation. Defibrillation was successful, but the patient remained hypotensive for approximately 15 minutes.

On the first postoperative day the urine output for eight hours was only 20 ml. On the second postoperative day, gasping respirations and slowing of the heart rate occurred transiently and seemed to respond to intravenous glucose and insulin. The potassium level rose to 7.2 mEq. The patient died 60 hours postoperatively during a period of asystole not responsive to cardiac massage.

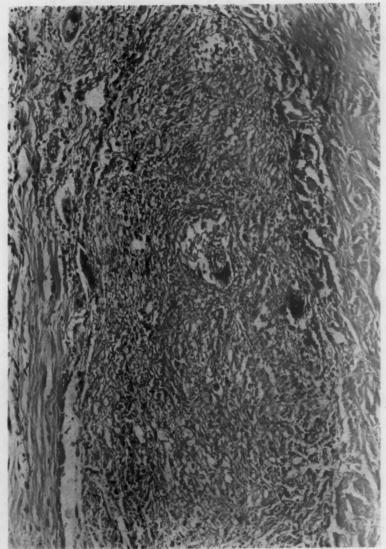
Autopsy Findings: The significant pathologic processes were confined to the heart, lungs, liver, spleen and lymph nodes. The cardiac dilatation and passive hyperemia of lungs, liver and spleen were consistent with the terminal congestive heart failure. Nondeforming tricuspid valvulitis, slight mitral stenosis and slight aortic stenosis were stigmata of chronic rheumatic valvulitis in this 405 gm. heart

(figure 3). Subendocardial hemorrhages below two of the commissures of the aortic valves were probably related to the recent valvulotomy. Verrucae were not observed along the line of closure of the mitral valve. The endocardium was glistening and translucent. On section, the myocardium was reddish brown, moderately firm and grossly unremarkable. No granulomas were visible in the region of the membranous septum, lungs, liver, spleen or lymph nodes. The lymph nodes were not enlarged.

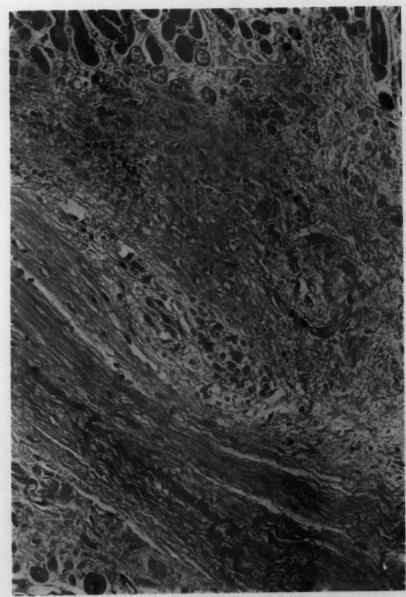


Fig. 3. Gross photograph of the heart demonstrating moderate thickening of the aortic leaflets, fusions of the right coronary posterior commissure and cardiac hypertrophy.

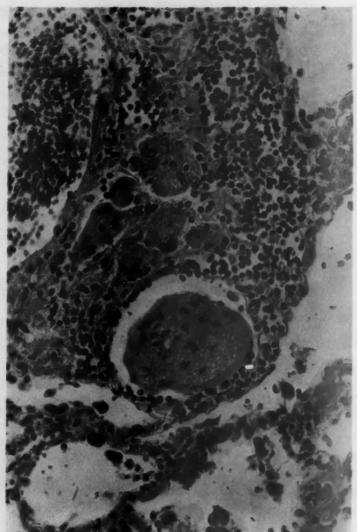
Microscopic examination, however, revealed that the atrioventricular node and bundle had been destroyed by granulomatous inflammation (figure 4). The granulomas were composed of multinucleated giant cells, epithelioid cells, lymphocytes and dense connective tissue. The latter infiltrated rather than surrounded the granulomas. Asteroid bodies and vacuoles were frequently observed in the giant cells. A solitary similar granuloma was observed adjacent to a venule in the epicardial fat. Located also in the interventricular septum and the posterior wall of the left ventricle were occasional spindle-shaped Aschoff bodies. These were composed of fragmented coarse collagen fibers with enmeshed pyknotic Aschoff cells, Anitschkow myocytes and occasional lymphocytes (figure 5).



Replacement of the atrioventricular node by multinucleated giant cells, epithelioid cells, lymphocytes and connective tissue. A few remaining muscle fibers are in the lower portion of the field. (×173).



Perivascular Aschoff body in the left ventricle with moderately polarized connective tissue, multinucleated Aschoff cells and Anitschkow myocytes. (×225) FIG. 5.



Perivascular granuloma in the lung composed of numerous giant cells containing asteroid bodies and vacuoles, epithelioid cells and lymphocytes.  $(\times 635)$ 

Small focal granulomas similar to those in the atrioventricular node were observed in the lungs, liver, spleen and lymph nodes (figure 6). In view of the distribution of the granulomas, the absence of caseous necrosis and birefractive crystals, and negative stains for acid-fast bacilli and fungi, this granulomatous inflammation was interpreted as sarcoid.

#### DISCUSSION

This patient's medical management was difficult because of the failure to control her periods of asystole by atropine, sublingual and intravenous Isuprel, hydrocortisone and molar lactate. The decision to perform aortic valve surgery was made in a desperate attempt to improve coronary artery blood flow, presumably reduced from tight aortic stenosis. At postmortem examination it was found that the aortic valve was not sufficiently stenosed for valvulotomy to have been of assistance in increasing coronary flow. Hyperkalemia might have been an unrecognized factor in this patient's terminal episode. Levels of 9 to 11 mEq./L. may cause asystole when sinus rhythm has been present. However, levels as low as 6.3 mEq./L. have been reported to cause asystole when complete A-V dissociation is the initial rhythm.<sup>1</sup>

In this case, myocardial sarcoid was confined to the atrioventricular node, atrioventricular bundle and a solitary epicardial granuloma. The granulomas in the lung, liver, spleen and lymph node were microscopic. Although slight in extent, the sarcoid was strategically located in a structure of vital physiologic importance, i.e., the atrioventricular node, and thus caused complete heart block.

The clinical significance of the Aschoff body is equivocal. The occasional polarized and fibrillar Aschoff bodies observed in this case were morphologically similar to the senescent bodies discussed by Tedeschi et al.<sup>2</sup> Whether this truly represents senescence or a smoldering process in a patient with altered reactivity cannot be determined.

Varying degrees of A-V block, excluding that secondary to vagus impulses and drugs, are in the great majority of cases seen in arteriosclerotic, hypertensive and rheumatic heart disease.<sup>8</sup> In young or early middle aged people, however, complete A-V dissociation presents a somewhat different problem in diagnosis. Any lesion that may interrupt the myocardial conducting system may cause heart block.

An incomplete classification of the common causes of complete heart block in the younger age group may include the following:

- I. Acute infectious disease
  - A. Diphtheria 4, 8
  - B. Rheumatic fever (rarely) 6, 7
- II. Postinfections
  - A. Rheumatic heart disease, usually older age group 8
  - B. Diphtheria
- III. Chronic granulomatous disease
  - A. Sarcoid 10, 11
  - B. Syphilis
- IV. Congenital
  - A. With septal defects 12
  - B. Without septal defects 18

V. Carotid sinus hypersensitivity

VI. Postcardiotomy repair septal defects 14, 15

VII. Idiopathic

In the search for a diagnosis of the cause of heart block in this younger age group, the usual diagnostic aids of history, physical examination and routine laboratory work, including serology, roentgenograms and electrocardiograms, are useful. In addition, special studies may be necessary. A positive Schick test is helpful in that it indicates no previous exposure to Corynebacterium diphtheriae sufficient to produce immunity and, unless there is a recent history suggesting diphtheria, excludes this etiologic possibility. Sarcoid may be suspected if sarcoid has been proved to exist elsewhere in the patient, if the Kveim test is positive, <sup>16</sup> or if scalene node biopsy reveals nonspecific granulomatous inflammation. Even if done under local anesthesia, the latter procedure may be dangerous in a patient with complete atrioventricular dissociation because of the inherent possibility of cardiac asystole. After all diagnostic procedures are exhausted, the etiology of the block may still be only suspected, and may not be found even by careful autopsy examination.

Sarcoid may involve the heart directly, or secondarily as a result of pulmonary disease. Pulmonary sarcoid may cause fibrosis, pulmonary hypertension and cor pulmonale. Longcope and Freiman observed myocardial sarcoid in 20% of the autopsied cases of sarcoidosis reported in the literature up to that time. Richer and Clark found two cases of myocardial sarcoid in their 22 autopsied cases of sarcoid. Peacock et al. recently reviewed 29 autopsied cases of myocardial sarcoid. Electrocardiographic manifestations included paroxysmal tachycardias, conduction defects and left ventricular hypertrophy. Ten of the patients died suddenly, and 14 had Stokes-Adams attacks or other clinical features of heart block. Death from myocardial involvement occurred from three months to 15 years after the onset of clinical symptoms.

## SUMMARY

A patient with complete A-V block secondary to sarcoid of the conducting system is presented. In addition, there was rheumatic carditis with focal Aschoff nodules and minor involvement of the aortic, mitral and tricuspid valves. The etiological factors of atrioventricular dissociation in the young adult are discussed.

# · ACKNOWLEDGMENT

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## SUMMARIO IN INTERLINGUA

In juvene adultos, bloco cardiac complete pone frequentemente un difficile problema diagnostic e therapeutic. Es presentate un caso que illustra ille difficultates.

Le patiente esseva un femina de racia blanc de 32 annos de etate qui habeva habite episodios de syncope e bradycardia depost sex menses. Post su hospitalisation, il esseva trovate per electrocardiographia que illa habeva un complete bloco cardiac. Esseva etiam notate indicationes physic e radiologic pro stenosis aortic. Asystole occurreva frequentemente e non esseva regulabile per atropina, Isuprel intra-

venose, hydrocortisona intravenose, o molar lactato de natrium intravenose. Le tentativa de augmentar le fluxo coronari verso le myocardio e le systema de conduction per medio de valvulotomia aortic remaneva sin successo. Le patiente remaneva con bloco cardiac e moriva 60 horas post le operation. Al necropsia le constatation inusual esseva facite que le nodo e le fasce atrio-ventricular esseva destruite per sarcoide. In plus, myocarditis rheumatic e leve grados de stenosis aortic esseva trovate.

Le causas commun de bloco cardiac complete in subjectos de plus juvene gruppos de etate es classificate. Es discutite le methodologia pro le diagnose del causa de bloco cardiac in iste gruppos. Studios special de utilitate possibile es le test de Schick, le test de Kveim, e biopsia de nodo scalen. Iste ultime manovra es riscose, mesmo quando effectuate sub anesthesia local, a causa del inherente possibilitate de asystole cardiac. In un certe numero de casos, nulle etiologia pote esser determinate in despecto del plus meticulose examine necroptic.

Es presentate un breve revista del litteratura relative a sarcoide myocardial, con attention special prestate al incidentia de bloco cardiac, al manifestationes electrocardiographic, e al modo del morte.

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# EDITORIAL

STANDARDS OF PRACTICE OF INTERNAL MEDICINE: METHODS OF JUDGING ITS OUALITY IN HOSPITALS

GENERAL interest in evaluating the quality of medical performance in the hospitals of this country has increased significantly during the last decade or so. Among the reasons for this are a fourfold increase in the number of hospital admissions during the last 30 years (table 1), growing initiative by various medical organizations, and availability of federal funds for hospital construction and research project grants.

Appraisal of the quality of medical practice must be done by physicians, of course. With increasing specialization each group must judge (or develop methods for others to judge) the performance of their colleagues. The pioneering efforts by the American College of Surgeons in this field are well known. Dating back to 1918, they are generally acknowledged to have resulted in vast improvement in hospital practice. More recently this program has been carried out by the Joint Commission on Accreditation of Hospitals. The American College of Physicians has contributed financially and administratively to the Commission's activities but little of a creative character has emanated from internists as a group.

In addition to the programs developed by the College of Surgeons and the Joint Commission, more recent studies have been undertaken by the agencies shown in table 2 in the fields and locations indicated for each. They are both general and specialized in character and include the one in internal medicine reported herein. References to previous reports on each of them are given in the table. An excellent review of the purposes and current status of each of these studies and of evaluation problems in general is contained in a recent report by a special committee representing the Department of Medicine and Surgery in the Veterans Administration.<sup>1</sup>

It is the consensus of opinion among informed students of the subject that reliable and valid methods of measuring the quality of medical care objectively do not yet exist. There is doubt that they can be devised for use even within a given specialty. It is obviously most difficult to quantitate quality. On the other hand, there is good reason to believe that virtually all effort to appraise quality leads automatically to improvement in medical care even though the validity of the methods used is not established.

<sup>\*</sup> Report of the Committee for the Study of Hospital Standards in Medicine, supported

by grant W-79 to the American College of Physicians by the Division of Hospital and Medical Facilities, National Institutes of Health, U.S.P.H.S.

<sup>1</sup> Fellows, W. W., Zink, L. A., Barnwell, J. B., Fauber, J. E., and Peck, C. P.: Report of the Committee on Measurement of the Quality of Medical Care, Department of Medicine and Surgery, Veterans Administration, Washington 25, D. C., April, 1959.

TABLE 1 Total Physicians and Hospital Admissions in United States, 1928-1958

Year	Number of Physicians* (thousands)	Annual Admissions† (thousands)	Annual Admission per Physician
1928	153	5,700‡	37.2
1938	174	9,421	54.1
1948	198	16,821	85.0
1958	228	23,697	103.9

\* Am. M. Directory 20: 12, 1958. (Data for 1928 and 1948 interpolated.)
† Courtesy Vernon Weckwerth, A.H.A.

From average daily census and estimated length of stay.

Improvement as a primary goal is accomplished even though quality has not been measured reliably.

Physicians now treat about three times as many patients in hospitals as they did 30 years ago (table 1). Concurrently there has been rapid growth in the number of practicing internists (table 3). Judging by data from 25 representative hospitals the increase in the number of medical cases admitted to hospitals has been in proportion to the total (table 3). One reason for the present world leadership held by the American medical profession has been the enormously increased effectiveness of diagnosis and management of disease in hospitals by internal medicine as a specialty.

TABLE 2 Current Studies of Quality of Patient Care in American Hospitals

Responsible Agency	Field of Study	Headquarters	Date of Origin	Reference
Committee on Professional and Hospital Activities	General	V. N. Slee, M.D., 201 S. Main St., Ann Arbor, Mich.	1953	Modern Hosp. 86: 62, 1956; July, 1956; June, 1957
American College of Physicians	Internal Medicine	G. K. Fenn, M.D., 122 So. Michigan, Chicago	1955	Ann. Int. Med. 47: 367, 1957; 49: 959, 1958; 49: cvi, 1958
Veterans Administration	Psychiatry	Mt. Alto VA Hospital	1956	Committee Report: D.M.&S., VA, Wash., D. C., 1959
Ohio State University	General	Engineering Exp. Station, O.S.U., Columbus, Ohio	1956	Progress Report N.I.H. GN-4784, 1958
Veterans Administration and National Institutes of Health	Psychiatry	VA Hospital, Perry Pt., Md.	1958	Am. J. Psychiat. 113: 122, 1956
Columbia University	General Med. and Pub. * Health	Sch. Pub. H. and Adm. Med., Columbia Univ.	1958	Medical-Hospital Research Digest, Washington, D. C., 1958

Thus, three reasons for a comprehensive study of standards of hospital practice in internal medicine are apparent, viz., rapidly increasing numbers of internists in practice, increase in their usage of hospitals, and an urgent need for methods of judging quality of medical practice by agencies such as the Joint Commission on Accreditation of Hospitals. Accordingly, in 1955 Leroy Sloan, then simultaneously president of the American College of Physicians and chairman of the Joint Commission, appointed a committee of College members \* to determine how best the quality of medical (as distinct from surgical) practice could be appraised in the hospitals of this country. It was considered axiomatic that efforts to evaluate the quality of patient care could not fail to lead to its improvement regardless of the

TABLE 3 Number of Internists and Total and Medical Admissions to U. S. Hospitals, 1928-1958

Year Reported Internists <sup>1</sup>	A.C.P. Members <sup>3</sup>	A.B.I.M. Certified	Annual Admissions to 25 Representative Hospitals			
accorded		memocro	Ceremeu	Total <sup>5</sup>	Medical <sup>6</sup>	% Medical
1928 1938	Unavailable	1,811 3,902	0 1,974	341,579	65,571	19.2
1942 1948	8,3252	6,250	5,508	389,377	71,052	18.2
1950 1958	12,079 18,687	10,289	12,160	472,096	98,250	20.9

<sup>1</sup> Am. M. Directory 17: 226, 1942; 18: 12-13, 1950; 20: 14-15, 1958. Courtesy W. R. Livingston, Chicago.

agricon, Chicago.

3 Including pediatricians.

3 American College of Physicians, courtesy E. R. Loveland, Philadelphia.

4 American Board of Internal Medicine, courtesy Wm. B. Werrell, Madison.

5 J. A. M. A. 110: 986–1048, 1938; 137: 1397–1455, 1948. J. Am. Hosp. A. 32: 11–220,

1958. 6 J. A. M. A. 111: 832-835, 1938; 137: 47-52, 1948; 168: 570-577, 1958.

use of such information. The Joint Commission, handicapped by a dearth of reliable criteria for assessing general medical practice, indicated deep interest in the project.

Impressed with the complexity of its task, the committee's first decisions were (1) to try to gain insight and information by conducting a field study in a representative group of hospitals, and (2) to obtain financial support and a full time project director for such a study. Dr. Marion A. Blankenhorn of Cincinnati accepted the directorship in 1955 and after his death Dr. George Karl Fenn of Chicago succeeded in 1957. The Board of Regents appropriated \$37,000 from the College treasury (\$17,250 of which was later returned) to cover initial expenses, and grants of \$43,100 and \$32,337

<sup>\*</sup> Arthur R. Colwell, M.D., Chicago, chairman; C. Wesley Eisele, M.D., Denver; Eugene G. Ferris, M.D., New York; J. Murray Kinsman, M.D., Louisville; E. Hugh Luckey, M.D., New York. Ellsworth L. Amidon, M.D., Burlington, Vt.; Fuller B. Bailey, M.D., Salt Lake City; and Karver L. Puestow, M.D., Madison, Wis. later replaced Dr. Kinsman (resigned) and Dr. Ferris (deceased).

to continue the study were awarded by the Division of Hospital and Medical Facilities of the National Institutes of Health. Four years of continuous study are now coming to a close and no further funds will be required. This is a final report to College members and to the medical and hospital professions at large, of the committee's conclusions, with brief descriptions of the character of the studies responsible for them.

Surveys: During 1956 and 1957 two separate field studies were conducted under the two Directors by 33 committee and other volunteer College members\* in 167 hospitals of various sizes and types in different parts of the country. These hospitals, selected and invited at random, were eager to participate in and contribute to the study. They will not be named here but their location is shown in figure 1. Forty-three of them were visited twice—once in each phase of the survey (vide infra). At least one full day was spent in each hospital by each surveyor, whose expenses and a modest honorarium were paid from the committee's grant funds.

The first survey has been described in detail by Blankenhorn.<sup>2</sup> Briefly, in 102 hospitals visited by 21 surveyors the records of 2,010 patients were reviewed and various medical, nursing and administrative staff members interviewed. Detailed information was recorded on especially designed punch cards from individual records, some by the record librarian and some by the surveyor. The Director tried to find a correlation between the quality of performance in each hospital as judged (1) by the surveyor from his interviews and reviews of patients' records and (2) by a variety of factual items of information taken from patients' records without interpretation.

It was concluded from this study that the quality of practice of general medicine in hospitals can be judged by study of a variety of patients' records by physicians who are well-trained and experienced as internists, and that evaluation of its own work by a hospital's staff is the most promising technic of appraisal.

The second phase of the survey has been described by Fenn.<sup>8</sup> Briefly, in 105 hospitals, 43 of which had been visited in the first survey, 25 committee and other members of the College again interviewed key personnel and reviewed about 2,000 individual patients' records. In this survey, however, attention was focused on the hospitals' efforts to assess the quality of

<sup>\*</sup>Thomas Almy, M.D.; Ellsworth L. Amidon, M.D.; Fuller B. Bailey, M.D.; Marion A. Blankenhorn, M.D.; William Bunn, M.D.; Alex M. Burgess, Sr., M.D.; Arthur R. Colwell, Sr., M.D.; Thomas J. Coogan, M.D.; Hugh L. Dwyer, M.D.; C. Wesley Eisele, M.D.; G. Karl Fenn, M.D.; Eugene Ferris, M.D.; Max Garon, M.D.; William Grace, M.D.; Julian Kaufman, M.D.; J. Murray Kinsman, M.D.; John C. Leonard, M.D.; E. Hugh Luckey, M.D.; Joseph McCarthy, M.D.; Frank McGlone, M.D.; Lawrence Minish, M.D.; S. M. Poindexter, M.D.; Karver L. Puestow, M.D.; Jack O. W. Rash, M.D.; Edward H. Reinhard, M.D.; Truman Schnabel, M.D.; Maurice Schnitker, M.D.; J. James Smith, M.D.; Charley Smyth, M.D.; Franz Stewart, M.D.; Maurice Strauss, M.D.; Henry E. Wilson, M.D.; Hugh R. Wood, M.D.

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Fig. 1. Location of 167 U. S. hospitals visited in field surveys in 1956 and 1957. Those now making trial use of the College plan are designated by the square symbols.

their own work. It was most encouraging to the committee to learn that in 118 of the 214 hospitals chosen for study the staffs were endeavoring on their own initiative to elevate their standards of internal medicine practice by study of their own hospitals' records. Consequently, 78 of them were visited in an effort to learn their methods of doing so. Surveyors made note of the best technics and tried to devise new ones for future general use.

In addition to this exploration a few of the most promising of the objective criteria previously studied were re-investigated, again with disappoint-

Table 4

Lack of Correlation Between Ratings of Individual Hospitals by Surveyors and Record of Autopsies, Consultations, and Staff Meetings

Autopsy Records

Hospital Rating by Surveyor	Range of Autopsy Percentage	Number of Hospitals				
		Over 50%	50-30%	30-20%	Under 20%	
Excellent Good Fair Poor	73 to 31.6% 62.6 to 20% 65 to 33% 40 to 7%	8 7 4 0	13 29 12 2	0 4 8 2	0 0 7 3	
		Consultation	n Ratio			
Rating	Range	Over 20%	20-15%	15-10%	Under 10%	
Excellent Good Fair Poor	67.3 to 8% 77 to 5% 52.4 to 3% 17.5 to 8.5%	8 11 2 0	5 16 6 1	6 6 13 1	1 5 12 3	
	Number	of Scientific A	Meetings Annua	lly		
Rating	Range	Over 50	50-25	25-12	Under 12	
Excellent Good Fair Poor	96 to 10 64 to 0 62 to 4 28 to 0	9 12 2 0	3 5 4 1	4 18 13 5	1 3 12 1	

ing results. Autopsy rates, staff meeting attendance, consultations, availability of a full time pathologist or radiologist, number of certified internists on the staff, and certain specific diagnostic and therapeutic measures were reëxamined critically. As shown in table 4, whereas certain trends were apparent, when applied to any given institution validity could not be established with confidence, so the "magic formula" concept was abandoned for a second time.

After almost three years of field work and efforts to validate appraisal methods in internal medicine the committee reaffirmed and expanded its earlier conclusions in 1958 as follows:

1. There are no simple objective criteria by which the quality of care of patients in general medicine can be judged in a hospital by an outside agency.

2. Nevertheless, by systematic, critical review of the records of patients hospitalized, competent clinicians can render reasonably satisfactory

judgments.

3. The quality of care received by patients must be assessed, not the quality of the record-keeping, indispensable as that is also.

4. This is best done by an appraisal committee composed of physicians on the hospital's own staff.

Staff education and resulting improvement in care of patients are the most desirable consequences of any such appraisal system.

The earnestness with which a hospital tries to evaluate its own practice can be used by a qualified outside agency to judge that hospital's performance.

Method of Evaluation: The next phase of the Advisory Committee's work was to develop and put to trial use a specific method, conforming to the principles outlined above, which any hospital could use to judge its own work in general medicine. This method was exhibited at the 1959 meeting of the College in Chicago. It is described in detail below.

## MEDICAL CARE APPRAISAL PLAN

Organization: A Medical Care Appraisal Committee will be formed by action of the hospital staff. It will be appointed by the President of the staff after consultation with the Chief of Medicine. The members of the Committee will be chosen from members of the hospital staff who practice general medicine or allied specialties. The membership of the Committee will be arranged so that one or two members of the Committee are replaced at stated intervals. All members of the staff who practice general medicine thus will be required to serve on the Committee in time. The size of the Committee will be governed by the number of medical admissions to the hospital and will be determined in the manner described below.

Purpose: This Committee will be concerned solely with evaluation and improvement of the quality of medical care. It will do this by a critical examination of the records of certain patients. It will have no other functions. It may comment on the quality of the records but will review them primarily for the purpose of judging or appraising the quality of medical care. Standards of practice of medicine will be elevated and maintained as a result of the Committee's activities. It is not the function of the Appraisal Committee to invoke penalties, and the Committee shall have nothing to do with any disciplinary action that may be required as a result of its

appraisals.

Number of Records to be Evaluated: In most hospitals it is impractical to examine all medical records fully and critically. The records of medical patients who die should be evaluated, as well as certain others, as specified below. Appraising will be done at monthly intervals at least. The number of records evaluated each month will be determined by the number of medical admissions to the hospital. So will the size of the Committee.

The number of live records selected for appraisal each month will equal 20% of the medical admissions to the hospital reduced to the nearest decade. For example,

if there are 273 medical admissions in a given month the 20% figure will be 54.6. Therefore, 50 records should be evaluated. If there are 192 medical admissions, the 20% figure will be 38.4. Therefore, 30 records should be evaluated. Should the 20% figure be 10 or less, 10 records should be evaluated. After the appropriate figure is obtained, the records of all medical patients who died during that month will be added.

Size of Committee: No Committee member should be required to review so many records that they are not appraised thoroughly. The number of staff members appointed to the Committee will be arranged so that no Committee member will be required to evaluate more than 10 or 12 records each month.

Selection of Records: The Committee will not concentrate its attention on the patients of certain physicians and no effort should be made specifically to select any particular records except as provided below. It should be the object of the Committee to examine during the year some records of every member of the staff who practices internal medicine or allied specialties.

It is recommended that the Committee select from the files and from the floors the required number of records in disease categories, as follows:

Diseases of the cardiovascular and renal systems Diseases of the endocrine glands and diabetes

Diseases of the endocrine glands and diabetes Diseases of the gastrointestinal tract

Diseases of the hematopoietic system Diseases of the liver and bile passages

Neurologic diseases and psychoneuroses

Diseases of the respiratory system

Rheumatic diseases

It is desirable to evaluate records from a different disease category each month. When the list has been completed the evaluations should be repeated by monthly categories again, but not necessarily in the same order.

If it happens that the required quota of records cannot be filled from the files or from the floors by a single disease category in a current month, other records in the same disease category from the files of the past six months may be added. If the quota is still not filled, another category may be added. If, for any reason, it is not feasible to examine the records by disease categories, records may be selected at random.

Evaluation of Records: The records selected should then be made the subject of a critical analysis of the quality of medical care. Regarding diagnostic procedure the following questions should be answered, among others:

Were the history and physical examination adequately presented? If the history and physical examination were performed prior to the admission of the patient to the hospital, did the hospital record contain an adequate transcript or rewrite?

Were physical findings properly judged and investigated?

Were the blood pressure and weight recorded?

Were the laboratory examinations appropriate, viz., was there too much or too little laboratory work?

Were laboratory findings properly assessed and utilized by the attending physician? (For example, if any unusual or unrelated laboratory finding appeared, was its cause investigated?)

Was the diagnosis justified and were collateral findings explained and inves-

Was there evidence that the physician in charge had good understanding of the condition represented?

Regarding management the following questions should be answered, among others:

Did the record demonstrate that the attending physician was reasonably familiar with current knowledge of the disorder under study and that treatment was properly applied?

Were errors and inconsistencies noted, with due respect for legitimate differences of opinion? (For example, did a patient on a low sodium diet receive intravenous salt solution?)

Was consultation employed when the diagnosis was doubtful or treatment

Was consultation used to investigate associated problems outside the field of internal medicine?

Was the consultant's opinion respected? Was treatment harmful in any way?

Were methods generally known to be ineffective used?

Was accurate diagnosis properly attempted before treatment was given? Was there evidence of unnecessary surgery or other needless therapy?

Were avoidable time and expense incurred?

Reports: A written report \* will be made for each record reviewed. These reports should be kept confidential, identified only in code or not at all. The names of the patient, attending physician and appraising physician should not appear in the report. The report should not be filed with the record, but should be available only to the Appraisal Committee and the executive committee of the staff. It is recommended that these reports be destroyed as soon as their purpose has been served.

Staff Action: It is recommended that the general results of the evaluation be presented for discussion by members of the Committee at monthly intervals before the entire medical department or staff. Although it is impractical to discuss all records, differences in diagnostic and therapeutic procedures within given disease categories may be brought out. The validity of certain technics may be questioned. Omissions may be pointed out. Certain records that demonstrate exceptionally good diagnostic or therapeutic skill should also be presented on occasion.

Discussions such as these are extremely important. With anonymity of patients, attending physicians and reviewing physicians rigorously preserved, the discussions can be free, frank and open. They will do much to elevate standards of medical

care regionally.

If the Committee should discover gross mismanagement, little will be gained and much may be lost by presenting such instances before the general staff for discussion. Such records should be evaluated carefully by the entire Committee and the findings transmitted to the executive committee of the staff.

It will be the duty of the executive committee to determine whether or not disciplinary action is necessary, and if so to impose appropriate penalties.

This plan, still in a tentative form, is being revised continuously. Although by its use instances of mismanagement or sub-standard practice may be discovered automatically, the method is not intended primarily to seek them out. Rather, it suggests an evaluation technic that will benefit every member of the hospital staff who practices general medicine. If appraisals are made critically the advantages which should accrue are: (1) greater

<sup>\*</sup>Figure 2 shows the appraisal form recommended for this purpose by the Advisory Committee. It contains space for a narrative report and opinion by the appraising physician. It does not call for information regarding completeness of the record.

# THE AMERICAN COLLEGE OF PHYSICIANS STUDY OF HOSPITAL STANDARDS IN MEDICINE

## APPRAISAL FORM

Age of Patient	Condition	on Discharge	
RIMARY DIAGNOSIS			
THER SIGNIFICANT	T DIAGNOSES		
. History	Adequate	Inadequate	
	If inadequate, how or	why	
Physical examination	Adequate	Inadequate	1.24
	If inadequate, how or	why	
Laboratory examination	Adequate	Too much	Too little
	Were laboratory finding	ngs properly evaluated and util	ized
Diagnosis	Was admission diagno	us justifiable	
	Was discharge diagnor	is proven	
Management	Adequate	Inadequate	If inadequate, please discuss under 9 below
Consultation	Properly employed	Improperly withh	eld
	Admission nate		
Notes by Attending Physician	Progress, notes		
, and a distribution of the same of the sa	Discharge Summary_		
Quality of record	-		
Remarks			
. Final Appraisal of	Acceptable	Unacceptable	Unable to judge

(Where the quality of care is considered inadequate, at least two members of the Committee should study and judge the record. If they agree and the record is graded less than acceptable it should be brought to the attention of the entire Committee.)

May 1, 1918

Fig. 2. Form for recording results of appraisals of individual patients' records.

insight for Appraisal Committee members resulting from their own work; (2) better performance by the staff in general by virtue of Committee reports and discussions of selected instances of good and bad performance in staff meetings, and (3) elevation of standards due to awareness of all concerned that the quality of medical practice is an object of systematic attention.

Trial Use of Appraisal Plan: During most of 1958 and 1959, 55 of the hospitals shown in figure 1 made actual use of this plan in practice. They made critical suggestions for its improvement and have now submitted anonymous reports on 8,703 patients to the Director of the project. He has noted their effectiveness and faults and summarized their findings. Together with the Advisory Committee he has consulted freely with the chairmen of appraisal committees, making occasional changes in the technics

of operation and report.

During this final phase of the Advisory Committee's work two observations have been most encouraging, both confirming the need which was apparent at the time the project was begun. First, the hospitals surveyed and used to try out the plan have been most interested, coöperative and helpful in the main. Each participating member of their medical and administrative staffs shares the Committee's gratitude for his support and advice. Second, many other physicians and hospitals, upon learning of the project from its meager reports and in visits to its exhibit, have shown intense interest, usually seeking help for initiating similar activities locally. Indeed, for that reason it has been difficult to confine the pilot study of the Appraisal Plan to the hospitals selected, yet this has been done in the interests of coöperative study and development. The Committee has felt that it and the College it represents are in no position to make wide application of any evaluation method. The Committee's charge was to devise a method, not apply it.

Publicity: As the project has matured it has become evident that the American College of Physicians deserves public recognition for this crusade to elevate standards of general medical practice in hospitals. Further, if any such plan as the one reported here is to be applied generally hospitals and physicians should be informed of its need and content. Accordingly, the Board of Regents has approved a recommendation that: "Popularized descriptions of the plan and its objectives should be published in appropriate medical and hospital journals and news items released to medical news sections in national journals, particularly those devoted to internal medicine and general practice." \* Notice by the lay press is considered likely to

follow.

Final Action: The Committee responsible for this study and plan will make a final report to the College at its meeting in November 1959, probably about the time this paper is published. A revised Appraisal Plan and Report Form will be presented for specific approval and presentation to the Joint Commission on Accreditation of Hospitals. If acceptable to both organizations it may then be applied generally by the Commission. In that event this Committee anticipates that hospitals' standards of general médical performance will be judged by the earnestness and zeal with which they

<sup>\*</sup> From report of Committee to Board of Regents in Chicago, April 19, 1959.

appraise their own practice. Judgments, both by the hospitals' staffs and by any outside agency, are inevitable.

## SUMMARY

1. Interest in judging the quality of general medicine practice in hospitals has increased within recent years. Attention to it will result in improvement in standards.

2. A committee of the American College of Physicians has completed a four year study of the problem. This is a narrative report of several phases of its study, including two field surveys and development and actual use of a specific appraisal plan.

3. Devised for hospital staffs to judge their own work in Medicine, a "Medical Care Appraisal Plan" and form for report are described in detail.

4. If the committee's report is approved by the College the plan will be offered to the Joint Commission on Accreditation of Hospitals for possible general application. In that event hospitals' performance in general medicine will be judged by the earnestness with which they appraise their own practice.

ARTHUR R. COLWELL, SR., M.D., and GEORGE KARL FENN. M.D.

122 S. Michigan Ave. Chicago c/o Dr. Fenn

# REVIEWS

Inborn Errors of Metabolism. By DAVID YI-YUNG HSIA, M.D. 358 pages; 15.5 × 23.5 cm. The Year Book Publishers, Inc., Chicago. 1959. Price, \$9.50.

The need for this book is apparent. The rapid expansion of knowledge about these anomalies has left ordinary physicians mystified and inclined to neglect the whole subject as hopelessly complex. When the term "Inborn Errors of Metabolism" was proposed in 1908, four such errors were known. Now it appears that there are more than 50, and other conditions may be added to this number as more is learned about the chemical defects that cause them. The book begins with a chapter summarizing the principles and terminology of human genetics. The known inborn errors of metabolism are described as disturbances in molecular structure (such as sicklemia), in molecular synthesis (such as agammaglobulinemia), in molecular function (such as galactosemia); and disturbances in renal transport mechanisms. Each of the errors of metabolism is described as simply as possible. The clinical features, heredity, pathogenesis, diagnosis, and treatment are reviewed, with references at the end of each description. Each subject is illustrated with pedigrees and photographs where possible, and an effort is made to connect the chemical defects with the genetic causes, with the help of diagrams. The appendix describes the easier laboratory tests and gives reference to the more difficult ones.

There are few adverse criticisms to make. One illustration seems to be reversed. The chapter on defects in blood-clotting may be simplified too much. The terms penetrance and expressivity are unfamiliar to some readers and should be defined. Of course specialists in metabolism are likely to disagree with some of the ideas in the book. But from the point of view of most readers the presentation is excellent. The style is clear and the explanations can be understood. The book is recommended to physicians who may encounter hereditary diseases and to students

who want a wide survey of this field.

GRANGE S. COFFIN. M.D.

Systemic Lupus Erythematosus. Edited by George Baehr, M.D., and Paul Klemperer, M.D. 84 pages; 18 × 26 cm. Grune and Stratton, New York. 1959. Price, \$3.75.

This monograph on Systemic Lupus Erythematosus is compiled by past or present staff members of Mount Sinai Hospital, New York, and every contributor is a recognized authority on his subject. It provides an up-to-date account of the disease and an excellent bibliography is included. Separate chapters are devoted to the pathology, pathogenesis, clinical features, and therapy of the disease. In the chapter devoted to the clinical features of the disease, no mention is made of the nephrotic syndrome in an account which is otherwise so complete. A passing reference might also have been made to the development of amyloidosis in long standing cases.

The inter-relationsh, of systemic lupus and rheumatoid arthritis is commented on, as is the finding of L. E. cells in rheumatoid arthritis and the presence of the rheumatoid factor in the serum of some patients with systemic lupus. These two diseases are still differentiated, although they have much in common. The presence of L. E. cells in a patient with a deforming arthritis identical to rheumatoid is not sufficient reason to change the diagnosis to that of systemic lupus. Many of the long survivals reported in systemic lupus and quoted in this monograph should be regarded

as cases of rheumatoid arthritis showing the presence of L. E. cells. If similar diagnostic criteria were adopted for systemic lupus as already are in use for rheumatoid arthritis, a much more accurate idea as to prognosis would emerge. Renal involvement is regarded as a lethal complication with an unremitting course; it is encouraging, therefore, to report the histological improvements which have been reported in the last few months following therapy with prolonged and large doses of steroids.

This monograph will be of interest to all those involved in the field of rheumatology and related diseases.

W. K. C. M.

Advances in Electrocardiography. Edited by Charles E. Kossmann, B.S., M.D., Med. Sc.D., F.A.C.P., Associate Professor of Medicine, New York University College of Medicine. Grune & Stratton, New York. 1958. Price, \$9.75.

There are available ever increasing numbers of texts devoted to electrocardiography. However, few have the same purpose as this one, i.e., "to familiarize the student with the most recent advances in electrocardiography considered to be of the

greatest immediate or future significance."

The contributors to this monograph participated in a course given in 1956 by the faculty of the New York College of Medicine, and the New York University Post-Graduate Medical School. They include, in addition to the editor, Dr. Adolph R. Berger, Dr. Morris Kleinfeld, Dr. Stanley A. Briller, Dr. Joseph V. Brumlik, and Dr. J. Marion Bryant. There are excellent, well illustrated sections devoted to the source of potential, conducting medium, electric field of the heart, spread of excitation and recovery in the normal and abnormal, and rhythms. The references are detailed, and the presentation scholarly. Advances in the field of electrocardiography have been rapid. This text attempts, with a great measure of success, "... to present, interpret, and integrate, so far as possible, these advances." It should prove of great value to the discerning student and internist.

L. S.

A Symposium on the Evaluation of Drug Toxicity. Edited by A. L. WALPOLE, Ph.D., B.Sc., and A. Spinks, M.A., Ph.D., B.Sc. 138 pages; 16 × 24 cm. Little, Brown and Co., Boston. 1958. Price, \$5.50.

Many of the drugs which the physician routinely uses today may cause distressing and dangerous toxic manifestations even when used in the smallest doses. One need only mention new and potent steroids, antibiotics, phenothiazine derivatives, antimalarials, anticonvulsants, etc. We are in an era of new synthetic agents of great potency, and potency always carries the risk of serious side-effects. Use of potent medicaments requires that new drugs be studied more carefully than ever before, and vast amounts of data from animal experimentation must be reviewed by toxicologists, pathologists, pharmacologists, biochemists, clinicians, and many other specialists before the drug can be tried on human subjects. After the drug has been tried clinically or has found widespread use by practitioners, it is frequently necessary to reëvaluate it in the light of accumulated experience. This book is a record of a symposium, the theme of which was: The Evaluation of Drug Toxicity. It brings together a series of nine papers presented before a group of 46 distinguished medical scientists at a symposium organized for the opening of the new research laboratories of The Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, England, on October 1, 1957. Topics discussed were: Problems of Toxicity in Clinical Medicine (Wayne); Sexual Differences in the Toxicity and Therapeutic Action of Chemical Substances (Hurst); The Morphological Evaluation of Toxic Action (Paget); Determination of Efficacy and Safety of New Drugs (Litchfield); The

Testing of Drugs for Toxicity (Barnes); Allergic Reactions as Hazards in the Use of New Drugs (Davies); The Toxic Action of Drugs on the Bone Marrow (Jacobson); Some Experimental Studies on Toxic Liver Injury (Magee), and Actions of Drugs on Subcellular Structures (Judah and Rees). A verbatim transcription of the discussion following each paper with the names of the discussants is an especially valuable feature of the book. The book is well printed, beautifully illustrated and substantially bound. Since all persons participating in the symposium are active workers in the field of drug toxicity, the work may be regarded as an authoritative contribution to the literature of toxicology and as such will appeal to all concerned with the many problems encountered in the use and development of potent new therapeutic agents.

Pancreatitis: A Clinical-Pathologic Correlation, By Herman T. Blumenthal, Ph.D., M.D., and J. G. Probstein, M.D. 379 pages; 16 × 23.5 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1959. Price, \$9.50.

This small encyclopedic volume summarizes in appealing style what is known regarding pancreatitis. Though the book is intended primarily as a clinical-pathological correlation based solely on autopsy material, experimental studies are considered in relation to clinical problems. The authors present detailed analyses based

on personal experience with 163 autopsied cases of pancreatitis.

There are 19 chapters divided into five sections. In Part 1 the many etiologic factors, proposed as a result of clinical observations and experimental work, are reviewed from a statistical point of view. In Parts 2 and 3 the pathologic physiology and anatomy of pancreatitis are admirably covered. Here the authors have introduced the concept of goblet cell metaplasia occurring in the ductal epithelium of the pancreas as a protective mechanism. This transformation of ductal columnar epithelium to mucin producing goblet cells is viewed as an alteration representing protective responses to transductal irritants. In Part 4 the clinical manifestations of the disease are constructed from the foregoing. Finally, the therapy of acute pancreatitis and its sequelae are considered in Part 5. The extensive lists of selective references appended to each section confirm the voluminous literature reviewed for the presentation of this monograph.

The book is unique because there are no contemporary publications of similar magnitude devoted to the subject. Judging from medical literature, current researches on pancreatitis are absorbing increasing time and effort and, in this respect, the volume will be valuable to the student as a guide and reference. Moreover, as intended by the authors, it serves to focus attention on problems for future study in a fertile field. The book is enthusiastically recommended to the clinician, investi-

gator, and pathologist.

The Treatment of Diabetes Mellitus. 10th Edition, revised. By Elliott P. Joslin, Howard F. Root, Priscilla White, and Alexander Marble. 798 pages: 16 × 24 cm. Lea and Febiger, Philadelphia. 1959. Price, \$16.50.

J. E. K., Jr.

The first edition, by Dr. Joslin alone, appeared in 1916. This, the tenth edition of this celebrated volume, represents the condensation of the clinical experience of Dr. Joslin over two generations, and of his associates over a lesser period. Their experience derives from their personal observations and follow-up studies of almost 53,000 glycosuric patients, of whom about 43,000 had true diabetes mellitus. Among these 43,000 about 18,000 fatalities have been recorded, and among the surviving patients were 82 who had diabetes mellitus for 25 years without detectable evidence of those complications attributable to poor control of their disease.

The direct contribution of the senior author to this edition totals about 175 pages devoted to present concepts, incidence, etiology, prevention, diagnosis, classification, symptomatology, prognosis, and treatment of diabetes mellitus. His style is reminiscent, anecdotal, and conversational. He stresses the contributions of the clinicians of the pre-insulin era, as if to say with Campbell, "To live in the hearts we

leave behind, is not to die."

In 1917, in the preface of his second edition, Dr. Joslin wrote that, "The care of . . . (diabetic patients) . . . has devolved and will devolve almost wholly upon the general practitioners," and that, "any method of treatment, therefore, to be of maximum service must be simple alike for physician and patient, for the practitioner is a very busy man and the patient must clearly understand the reason for a Spartan life." In 1959, he writes that, "the treatment of diabetes mellitus, although still grossly inadequate is steadily improving in direct proportion to its degree of control. . ." He adds that, "the means for treatment of the diabetic are more adequate than ever, but the problem is how to put them in effect more generally." The years have seen the maintenance of his zealousness.

The effects of diabetes mellitus on organ systems and the interrelations of that disorder with other organ-system disorders, and the therapeutic and prognostic

problems arising therefrom, are detailed in approximately 250 pages.

Dr. White succinctly summarizes, in 62 pages, her experiences with "diabetic

children and their later life," and with "pregnancy complicating diabetes."

Although the emphasis throughout is on treatment, as the title states, Dr. Renold, in a 40-page chapter, covers selected physiologic and biochemical interrelations pertinent to diabetes mellitus. Applied physiology of insulin, blood sugar, and examination of the blood and urine in diabetes is dealt with by Dr. Marble. Dr. Warren and Dr. LeCompte again summarize the pathology of diabetes. Dr. Marble and Dr. Krahl evaluate conservatively the use of oral hypoglycemic drugs. Water and electrolyte metabolism are given expanded coverage by Dr. Nichols in the section on diabetic acidosis by Dr. Root. Sections on insulin allergy, hypoglycemia, and other topics have been kept current, as well.

New features of interest, but of lesser importance, are present. The authors have adopted the Somogyi-Nelson method for the determination of blood sugars for clinical purposes. There is, apparently, the admission of even the possibility that "the vascular complications of diabetes mellitus may be genetically determined along with the diabetes, but not a consequence of the metabolic disturbance." There may be, also, some diminution in the tendency toward that dogmatism inevitably arising in the writings of physicians in the course of their prodigious and prolonged clinical experience. The authors recognize the tremendous output of literature on diabetes

and regret their omission of some important contributions of others.

Typographic errors are few for a work of such magnitude and none are misleading. The format is pleasant. The glare of the coated paper will increase the use of the volume as a reference, but decrease its use in sustained study by students and practitioners.

This monumental work will continue its position as the backbone of all collec-

tions of treatises on diabetes mellitus.

PERRY FUTTERMAN, M.D.

October 1959

The Management of Emergencies in Thoracic Surgery. By John Borrie, M.B.E., Ch.M., F.R.C.S. (Eng.) F.R.A.C.S. 340 pages; 25 × 17 cm. Appleton-Century-Crofts, Inc., New York, N. Y. 1958. Price, \$10.00.

Mr. Borrie has compiled an authoritative review of emergencies which arise in thoracic surgery. In addition he describes many of the everyday procedures per-

formed by thoracic surgeons in an attempt to avoid emergencies or treat complications in surgical patients. The pathophysiology, clinical features, and management of each emergency condition or complication is lucidly and compactly covered.

The illustrations and duplications are well chosen and presented. The illustrations of various positions in postural drainage, for instance, should be seen by

everyone involved in surgery of the chest.

The entire monograph is well written and should be a "must" in reading for medical students and house officers, both in medicine and surgery. The general practitioner and internist should benefit greatly from having it available for reference.

R. A. C.

## BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- The Acute Radiation Syndrome: A Medical Report on the Y-12 Accident, June 16, 1958. ORINS-25, Biology and Medicine. Compiled by Marshall Brucer. Pages not numbered; 27.5 × 21.5 cm. (paper-bound). 1959. From the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission; work performed under Contract No. AT-40-1-Gen-33. Available from the Office of Technical Services, Department of Commerce, Washington 25, D. C., at \$1.00.
- Anatomy and Physiology. Vol. 1. Cells, Tissues, Integument, Skeletal, Muscular, and Digestive Systems, Blood, Lymph, Circulatory System. College Outline Series No. 98. By Edwin B. Steen, Ph.D., and Ashley Montagu, Ph.D. 332 pages; 21 × 13.5 cm. (paper-bound). 1959. Barnes & Noble, Inc., New York. Price, \$2.50.
- Les Anémies Hypochromes de l'Adulte: Étude Clinique et Hématologique. By Docteur André Bel; preface by Professeur P. Croizat and Docteur L. Revol. 501 pages; 24 × 16 cm. (paper-bound). 1959. J.-B. Baillière et Fils, Paris. Price, 3.200 fr plus le port.
- Atlas of Roentgenographic Measurement. By Lee B. Lusted, M.D., Associate Professor of Radiology, University of Rochester School of Medicine and Dentistry; and Theodore E. Keats, M.D., Professor of Radiology, University of Missouri School of Medicine. 176 pages; 28.5 × 18.5 cm. 1959. The Year Book Publishers, Inc., Chicago. Price, \$9.00.
- Blood Groups: Symposium Published in the British Medical Bulletin, Volume 15, Number 2, May, 1959. 85 pages; 28.5 × 22 cm. (paper-bound). 1959. Medical Department, The British Council, London. Price, \$3.25.
- Cancer: A Worldwide Menace. Some Facts and Figures on Its Occurrence in the United States and Abroad, Prepared for the Committee on Government Operations, United States Senate and Its Subcommittee on Reorganization and International Organizations (Pursuant to S. Res. 347, 85th Congress, and S. Res. 42, 86th Congress). 40 pages; 23.5 × 14.5 cm. (paperbound). 1959. Printed for the use of the Committee on Government Operations by the United States Government Printing Office, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 40¢.
- Cancer in Families: A Study of the Relatives of 200 Breast Cancer Probands. By Douglas P. Murphy, M.D., Emeritus Professor of Obstetrics and Gynecology,

- School of Medicine, University of Pennsylvania; and Helen Abbey, Sc.D., Assistant Professor of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University. 76 pages; 21.5 × 14 cm. 1959. Published for The Commonwealth Fund by Harvard University Press, Cambridge. Price, \$2.50.
- Cholera. By R. Pollitzer, M.D., George Williams Hooper Foundation, University of California, San Francisco, USA., etc.; with a chapter on World Incidence written in collaboration with S. Swaroop, Ph.D., M.P.H., Chief, Statistical Studies Section, World Health Organization; and a chapter on Problems of Immunology and an Annex written in collaboration with W. Burrows, M.D., Professor of Microbiology, University of Chicago, Chicago, Ill., U.S.A. 1,019 pages; 24 × 16 cm. 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, \$20.00.
- Coupes Horizontales du Tronc: Atlas Anatomique et Radiologique a l'Usage des Chirurgiens et des Radiologistes. Chaire d'Anatomie de la Faculté de Medecine de Paris (Pr Gaston Cordier). By RAYMOND ROY-CAMILLE; preface by Pr GASTON CORDIER. 122 pages; 42.5 × 33 cm. 1959. Masson & Cie, Paris. Price, 8.000 fr.
- Current Problems in Allergy and Immunology: Papers Dedicated to Béla Schick on the Occasion of His 80th Birthday. Edited by WILLIAM KAUFMAN. 992 pages; 25 × 17.5 cm. 1959. S. Karger, Basel. Price, \$14.40.
- Diabetic Manual. 10th Ed. By Elliott P. Joslin, M.D., Sc.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc. 304 pages; 20.5 × 13.5 cm. 1959. Lea & Febiger, Philadelphia. Price \$3.75.
- Diagnosis of Congenital Heart Disease: A Clinical and Technical Study by the Cardiologic Team of the Pediatric Clinic, Karolinska Sjukhuset, Stockholm.

  2nd Ed. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson. 866 pages; 26.5 × 18.5 cm. 1959. The Year Book Publishers, Chicago. Price, \$28.00.
- Expert Committee on Biological Standardization: Twelfth Report. World Health Organization Technical Report Series No. 172. 43 pages; 24 × 16 cm. (paperbound). 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Les Formes Viscérales des Phacomatoses. By Docteur Jean Schmitt. 279 pages; 24 × 16 cm. (paper-bound). G. Doin & Cie., Éditeurs, Paris. Price, 2.800 fr.
- Impairments by Type, Sex, and Age, United States, July 1957-June 1958: Statistics on the Number of Impairments by Type, Sex, Age, Major "Activity, and the Number Due to Injury. Based on Data Collected in Household Interviews During the Period, July 1957-June 1958. Health Statistics from the U. S. National Health Survey, Series B-9. 28 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢.
- Intern's Manual (Cook County Hospital). 2nd Ed. By Arthur Bernstein, M.D., Assistant Medical Superintendent Cook County Hospital, etc. 308 pages; 18.5 × 11 cm. (paper-bound). 1959. The Year Book Publishers, Inc., Chicago. Price, \$3.00.
- Joint WHO/FAO Expert Committee on Zoonoses: Second Report. World Health Organization Technical Report Series No. 169. 83 pages; 24 × 16 cm. (paper-

- bound). 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60¢.
- The Marxian Bacillus. By J. A. Osorio Lizarazo. 210 pages; 21.5 × 14.5 cm. (paper-bound). 1959. Magisterio Español, Madrid.
- Mechanisms of Hypersensitivity. Henry Ford Hospital International Symposium, Sponsored by the Henry Ford Hospital, Detroit, Michigan, and Held at the Hospital, March 27, 28, 29, 1958. Editors: Joseph H. Shaffer, M.D., Physician in Charge, Division of Allergy, Department of Medicine, Henry Ford Hospital; Gerald A. Logrippo, M.D., Associate in Charge, Division of Microbiology, Department of Laboratories, Henry Ford Hospital; and Merrill W. Chase, Ph.D., Associate Professor, The Rockefeller Institute for Medical Research, New York City. 754 pages; 24 × 16 cm. 1959. Little, Brown and Company, Boston, Price, \$18,50.
- Mental Health Problems of Aging and the Aged: Sixth Report of the Expert Committee on Mental Health. World Health Organization Technical Report Series No. 171. 51 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60¢.
- Mind If I Smoke? By Harold Shryock, M.A., M.D. 138 pages; 21.5 × 14.5 cm. 1959. Pacific Press Publishing Association, Mountain View, California. Price, 50¢ paper-bound; \$2.50 cloth-bound.
- The Molecular Basis of Evolution. By Christian B. Anfinsen, National Heart Institute, National Institutes of Health, Bethesda, Maryland. 228 pages; 23.5 × 15 cm. 1959. John Wiley & Sons, Inc., New York. Price, \$7.00.
- Neurological Complications of Lymphomas and Leukemias. (Publication Number 357, American Lecture Series; a monograph in The Bannerstone Division of American Lectures in Tumors, edited by David A. Karnofsky, M.D., Associate Professor of Medicine, Cornell University Medical College, New York, N. Y.) By Henry M. Williams, M.D., Henry D. Diamond, M.D., F.A.C.P., Lloyd F. Craver, M.D., F.A.C.P., and Herbert Parsons, M.D. 134 pages; 22.5 × 14.5 cm. 1959. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$5.75.
- Neuropharmacology: Transactions of the Fourth Conference, September 25, 26, and 27, 1957, Princeton, N. J. Edited by Harold A. Abramson, M.D., Research Psychiatrist, the Biological Laboratory, Cold Spring Harbor, etc. 285 pages; 24 × 15.5 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$5.00.
- Office Orthopedics. 3d Ed. By Lewis Cozen, M.D., F.A.C.S., Attending Orthopedic Surgeon, Cedars of Lebanon Hospital, Los Angeles, etc. 430 pages; 24 × 15.5 cm. 1959. Lea & Febiger, Philadelphia. Price, \$9.50.
- Pain: Problems Pertaining to the Transmission of Nerve Impulses Which Give Rise to Pain. Preliminary Statement. By W. Noordenbos, Surgeon-in-Charge, University Neurosurgical Department, Wilhelmina-Gasthuis, Amsterdam (The Netherlands). 182 pages; 23 × 15.5 cm. 1959. D. Van Nostrand Company, Inc., Princeton, New Jersey. Price, \$8.50.
- Pathology of Tumours of the Nervous System. By Dorothy S. Russell, Sc.D., M.A., M.D., F.R.C.P., LL.D., Director, Bernhard Baron Institute of Pathology, London Hospital, etc.; and L. J. Rubinstein, M.D., Lecturer in Morbid Anatomy, London Hospital Medical College; with a chapter on Tissue Culture in Relation to Tumours of the Nervous System by C. E. Lumsden, M.D., Pro-

- fessor of Pathology, University of Leeds, etc. 318 pages; 25.5 × 19 cm. 1959. The Williams & Wilkins Company, Baltimore. Price, \$13.50.
- Physiology of Prematurity: Transactions of the Third Conference, March 25, 26, and 27, 1958, Princeton, N. J. Edited by Jonathan T. Lanman, M.D., Department of Pediatrics, New York University-Bellevue Medical Center, New York, N. Y. 157 pages; 24 × 15.5 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.00.
- Practitioners' Conferences Held at The New York Hospital-Cornell Medical Center.

  Volume 7. Edited by William J. Grace, M.D., Director of Medicine, The
  St. Vincent's Hospital of the City of New York, etc.; foreword by E. Hugh
  Luckey. 275 pages; 21.5 × 14.5 cm. 1959. Appleton-Century-Crofts, Inc.,
  New York. Price, \$6.75.
- Preventive Medicine: Principles of Prevention in the Occurrence and Progression of Disease. Edited by Herman E. Hilleboe, M.D., Commissioner of Health, State of New York, Department of Health, Albany; and Granville W. Larimore, M.D., Deputy Commissioner of Health, State of New York, Department of Health, Albany. 731 pages; 24.5 × 16 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome, Held at Bard Hall, College of Physicians and Surgeons, Columbia University, New York, N. Y., November 6-8, 1958. Edited by Jack Metcoff, M.D. 284 pages; 28 × 22.5 cm. (loose-leaf, paper-bound). 1959. Sponsored by the National Kidney Disease Foundation, New York. Price, \$5.25, plus 14¢, total, \$5.39.
- Proceedings of the World Congress of Gastroenterology and the Fifty-ninth Annual Meeting of the American Gastroenterological Association, Washington, D. C., U.S.A., May 25th through 31st, 1958 (in two volumes). 1,363 pages (both volumes); 26 × 17.5 cm. 1959. The Williams & Wilkins Company, Baltimore. Price, \$20.00.
- Progress in Allergy. Vol. V. Contributors: St. V. Boyden, Copenhagen; L. Brent, London; M. M. Mayer, Baltimore, Maryland; Ö. Ouchterlony, Gothenburg; Z. Ovary, Baltimore, Maryland; W. D. M. Paton, London; and B. H. Waksman, Boston, Massachusetts. Edited by Paul Kallós, Helsingborg. 508 pages; 25 × 17.5 cm. 1958. S. Karger, Basel. Price, sFr. 82.—
- Radiation Therapy. By WALTER T. MURPHY, M.D., Director of Therapeutic Radiology, Roswell Park Memorial Institute, Buffalo, New York, etc. 1,041 pages; 26 × 17.5 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$25.00.
- Systemic Lupus Erythematosus: A Mount Sinai Hospital Monograph. Editors: George Baehr, M.D., and Paul Klemperer, M.D. Contributions to the Symposium by Members of the Staff of The Mount Sinai Hospital, New York: Baruch J. Davis, M.D., Gabriel C. Godman, M.D., Donald Gribetz, M.D., Walter L. Henley, M.D., Saul Jarcho, M.D., Stanley L. Lee, M.D., Abou D. Pollack, M.D., and Louis J. Soffer, M.D. 84 pages; 26 × 18 cm. 1959. Grune & Stratton, New York. Price, \$3.75.
- A Way of Life and Selected Writings of Sir William Osler, 12 July 1949 to 29 December 1919 (formerly titled Selected Writings of Sir William Osler). 278 pages; 20.5 × 13.5 cm. (paper-bound). 1959 (Dover edition, first published in 1958, an unabridged and unaltered republication of the work first published in 1951 by Oxford University Press). Dover Publications, Inc., New York. Price, \$1.50.

# COLLEGE NEWS NOTES

THE ROLE OF THE INTERNIST IN AN ACCREDITED TUMOR CLINIC

An announcement by the A.C.P. Committee on Cancer

It is becoming increasingly apparent that the internist is in a position to fill a valuable role on Tumor Boards or in Tumor Clinics. In some institutions a qualified internist will already be available. In others interested internists may be available, but as yet not fully qualified in the treatment of malignant disease. Provisions for a place on the Tumor Board of such a qualified individual and encouragement of the interest of internists should be made.

- In instances where a Tumor Board exists a qualified internist should be a member of the Board on an administrative level equal to a surgeon or radiotherapist.
- The internist can contribute to the Tumor Board by establishing diagnostic procedures and encouraging diagnostic education.
- 3. The internist may contribute in an active manner. His primary role in this problem would be concerned with chemotherapy, including hormone therapy. With the broadening scope and interests of the hematologists, an institution might include a hematologist as a member of the Tumor Board. The internist should be capable of managing malignant disease with chemotherapeutic agents, dealing with the complications of chemotherapy, and be active in investigation in the field of chemotherapy.
- 4. The internist would provide for palliative care in the management of the terminal phase of malignant disease. He has access to the type of medical facilities necessary for such management; he is familiar with the use of palliative agents, other than specific anti-tumor drugs.

In institutions where a qualified internist is not available, it is recommended that the surgeon and radiotherapist encourage interested internists to participate in Tumor Board activities and aid them in becoming more skilled in the management of malignant disease. Such encouragement could include: (a) provision for education of younger internists in malignant disease, (b) provision for the internist to visit other institutions in which internists are active in tumor work, (c) provide for his attendance at formal courses in malignant disease with specific respect to chemotherapy. The internist should also be encouraged to play an active role in the state division of the American Cancer Society.

# BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

Emanuel Goldberger, M.D., F.A.C.P., New York, N. Y., A PRIMER OF WATER, ELECTROLYTE AND ACID-BASE SYNDROMES, published by Lea & Febiger, Philadelphia, Pa., 1959, 322 pages.

William Kaufman, Ph.D., M.D., F.A.C.P., Bridgeport, Conn., CURRENT PROBLEMS IN ALLERGY AND IMMUNOLOGY, published by S. Karger, New York, N. Y., and Basel, Switzerland, 1959, 992 pages.

Werner Simon, M.D., F.A.C.P., Minneapolis, Minn., and Robert D. Wirt, M.D., Minneapolis, Minn., DIFFERENTIAL TREATMENT AND PROGNOSIS IN SCHIZOPHRENIA, published by Charles C Thomas, Springfield, Ill., 198 pages.

The Twenty-third Annual Meeting of The New Orleans Graduate Medical Assembly will be held March 7-10, 1960, with headquarters at the Roosevelt Hotel in New Orleans, La.

The Sixty-sixth Annual Meeting of the Association of Military Surgeons will take place at the Mayflower Hotel, Washington, D. C., November 9-11, 1959.

The Sixth International Congress on Diseases of the Chest, sponsored by the American College of Chest Physicians, will be held at the University of Vienna from August 28 to September 1, 1960, organized by medical societies of Austria.

For information, write Professor Dr. A. Sattler, Generalsekretar, American College of Chest Physicians, Wien IX, Frankgasse 8, Austria.

The American College of Cardiology will hold its eighth interim meeting at the Benjamin Franklin Hotel, Philadelphia, October 23–25, according to Dr. Gabriel F. Greco, Ozone Park, N. Y., member of the publication committee. This year for the first time the scientific sessions of the college will be concurrent with the 32nd annual meeting of the American Heart Association and will include a joint program. The college will conduct fireside conferences on the evening of October 23, in which A. H. A. members will participate jointly. On October 25, a panel on cardiac resuscitation will be presented jointly by the college and the association's council on clinical cardiology.

Programs may be obtained from Dr. Philip Reichert, Executive Director, A. C. C., Empire State Building, New York City.

The Fourth International Goiter Conference will be held July 5-9, 1960, in London, England, under the auspices of the London Thyroid Club and the American Goiter Association. The American Goiter Association plans to make available to worthy candidates a limited number of travel grants for participants of this meeting. Applications are available from John C. McClintock, M.D., 149½ Washington Ave., Albany 10, N. Y. Applications will be received until January 1, 1960.

Abstracts (not to exceed 400 words should be submitted in quintuplicate) of American papers to be considered for presentation should be sent to Dr. Joseph E. Rall, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md. by December 1, 1959.

## KAREN HORNEY CLINIC FELLOWSHIP

The American Institute for Psychoanalysis is offering a fellowship of \$5,000 to psychiatrists applying for the full course of psychoanalytic training in the Institute. The recipient of the fellowship will be granted \$2,500 per annum during the second and third years of the training period.

Physicians are eligible to apply who are graduates of a medical school accredited by the American Medical Association and who have completed a one-year general internship and a two-year psychiatric residency in hospitals approved by the Association.

Further information may be obtained from Miss Janet Frey, Registrar, American Institute for Psychoanalysis, 220 West 98th Street, New York 25, New York.

The Yale University School of Medicine and the Grace-New Haven Community Hospital announce the formal incorporation of the Yale-New Haven Medical Center aimed at expanded patient-care facilities of the university hospital services.

The 1959 national conference of the National Rehabilitation Association will be held at the Statler-Hilton Hotel, Boston, Mass., October 26–28, 1959. For further information write Mr. Edward D. Callahan, Massachusetts Rehabilitation Commission, 14 Court Square, Boston 8, Mass.

# FELLOWSHIP IN PULMONARY PHYSIOLOGY

A fellowship in pulmonary physiology for foreign doctors, particularly those from the United States, is again available at the Pulmonary Physiology Laboratories of the University of Nancy Medical Center, Nancy, France, under the direction of Dr. Paul Sadoul. This fellowship commences October, 1959, or in 1960. It is for at least six months and requires a cursory knowledge of the French language. It pays a bourse, or stipend, of about 40,000 francs per month.

For information, write directly to Dr. Paul Sadoul, Experimental Pathology Laboratory, 20 rue Lionnois, Nancy, France.

## CERTIFYING BOARD EXAMINATIONS

- AMERICAN BOARD OF DERMATOLOGY: Secretary, Dr. Beatric M. Kesten, One Haven Ave., New York 32, N. Y. Written examination in several cities, October 5, 1959. Oral examination in Oklahoma City, January 15–18, 1960. Final date for filing all applications was July 1, 1959.
- AMERICAN BOARD OF INTERNAL MEDICINE: Secretary-Treasurer, Dr. William A. Werrell, One West Main St., Madison 3, Wis. Oral examinations for candidates on the East Coast, November 6-7, 9-10, 1959. Final date for filing applications was March 1, 1959.
- AMERICAN BOARD OF RADIOLOGY: Secretary, Dr. H. Dabney Kerr, Kahler Hotel Building, Rochester, Minn. Examinations will be conducted at the Shoreham Hotel, Washington, D. C., December 6-9, 1959. Deadline for filing applications was July 1, 1959. Candidates examined in Diagnostic Roentgenology may expect to be examined in Physics. The Spring 1960 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 6-10. The obligatory examination for Nuclear Medicine will be postponed until after June 30, 1962. Until that time this examination will be optional for those who wish to be examined in Radiology or Therapeutic Radiology.
- AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Secretary-Treasurer, Dr. David A. Boyd, Jr., 102-110 Second Avenue, S.W., Rochester, Minn. Examinations: Chicago, October 19-20, 1959; New York City, December 14-15, 1959; San Francisco, March 14-15, 1960.
- AMERICAN BOARD OF PEDIATRICS: Secretary, Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa. Written examination, January 8, 1960, in 85 centers. Deadline for filing applications is December 1, 1959. Oral examination in five cities in 1960—date to be announced later.
- AMERICAN BOARD OF PATHOLOGY: Secretary-Treasurer, Dr. Edward B. Smith, Indiana University Medical Center, 1040-1232 West Michigan Street, Indianapolis 7, Ind. Examination, New Orleans, November 12-14, 1959. The

initial examination in the special field of forensic pathology will be held in New Orleans, November 13, 1959. Final date for filing for these examinations was October 1, 1959.

AMERICAN BOARD OF PREVENTIVE MEDICINE: Assistant Secretary-Treasurer, Dr. Tom F. Whayne, 3438 Walnut Street, Philadelphia 4, Pa. Examinations in three sections—Public Health, Aviation and Industrial, and Preventive Medicine. Written examinations to be held April, 1960. Exact date to be announced later.

## MEETINGS

November 16-19, 1959—Southern Medical Association, Atlanta, Ga. December 1-4, 1959—American Medical Association Clinical Meeting, Dallas, Tex.

Note change in date for
Pacific Northwest Regional Meeting
Portland, Ore.
to

November 20-21, instead of November 14

The American Psychosomatic Society will hold its 17th Annual Meeting at the Sheraton-Mt. Royal Hotel in Montreal, Canada, March 26-27, 1960.

The Program Committee would like to receive titles and abstracts of papers for consideration no later than December 1, 1959. Abstracts of two or three pages, in nine copies, should be submitted to the Program Committee at 265 Nassau Road, Roosevelt, N. Y.

The Aero Medical Association has changed its name to the Aerospace Medical Association. Their *Journal of Aviation Medicine* is now known as *Aerospace Medicine*.

The Annual Meeting of the Association of American Medical Colleges will be held November 2-4 at the Edgewater Beach Hotel in Chicago. The theme will be MEDICAL EDUCATION IN A CHANGING WORLD.

For further information, write to Dr. Ward Darley, F.A.C.P., Executive Director, Association of American Medical Colleges, 2530 Ridge Avenue, Evanston, Ill.

# INTERNATIONAL CONGRESS OF GASTROENTEROLOGY

The International Congress of Gastroenterology will meet in Leyden, Holland, on April 20-24, 1960.

Scientific workers in the field of Gastroenterology are invited to contribute lectures to the Congress. Lectures should apply to either pathology, pathological physiology, clinical aspects of the small intestine, hepatitis, cirrhosis hepatis (and their possible connection) or be devoted to a subject of the lecturer's choice in the field of gastroenterology.

The Florida Diabetes Association will hold its annual meeting October 29-30, 1959, at the Balmoral Hotel, Bal Harbour, Fla. Dr. Jerome W. Conn, F.A.C.P., Professor of Medicine, University of Michigan Medical School, will be one of the featured speakers.

## POSTGRADUATE COURSES

The American College of Chest Physicians will present the following post-graduate courses:

- 12th Annual Course on DISEASES OF THE CHEST, Park Sheraton Hotel, New York City, November 9-13, 1959
- 5th Annual Course on DISEASES OF THE CHEST, Ambassador Hotel, Los Angeles, December 7-11, 1959

Tuition for each course is \$100. For further information, write to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

# KENNY FOUNDATION SCHOLARSHIPS

The Sister Elizabeth Kenny Foundation is continuing its program of post-doctoral scholarships to promote work in the field of neuromuscular diseases. Each grant will provide a stipend of \$5,000 to \$7,000 a year, depending upon the scholar's qualifications.

Further information may be obtained from Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Incorporated, 2400 Foshay Tower, Minneapolis 2, Minn.

Dr. Paul Wood, O.B.E., (Melbourne), F.R.C.P. (London), Director, Institute of Cardiology, London, England, will present a course in cardiology at the Texas Medical Center, December 7-11, 1959, sponsored by the University of Texas Postgraduate School of Medicine.

## DR. HENRY C. BUSWELL AND BERTHA H. BUSWELL FELLOWSHIPS

The University of Rochester has established a program of postdoctoral fellowships to be awarded graduates of approved medical schools to enable them to pursue research in any of the departments of the School of Medicine and Dentistry. The Buswell Fellowships are intended to assist well qualified doctors of medicine to prepare adequately for academic careers.

Buswell Junior Fellowships will be awarded to medical graduates who have completed at least one year of internship or equivalent training. Research experience is not required but will be of advantage to applicants. Research interest and promise are essential since Junior Fellows are expected to spend about 90% of their time in research or in advanced study in preparation for research. Buswell Junior Fellowships will provide a basic stipend of \$4,500 to \$6,000 per year, depending upon training and experience, and may be renewed with increments for a second or third year. An additional sum of \$500 per year may be provided for each dependent.

Buswell Senior Fellowships will be awarded to medical graduates who have held a Buswell Junior Fellowship for two or three years or have had comparable experience in medical research and wish to continue in an academic career. Buswell

Senior Fellowships will provide a basic stipend of \$5,500 to \$8,000 per year, depending upon training and experience, and with provision for annual increments. An addi-

tional sum of \$500 per year may be provided for each dependent.

Applications will be received at any time. Awards will be announced periodically. A Fellowship may be activated at any time during the year after announcement of award. Additional information and application forms may be obtained from Chairman, Committee on Buswell Fellowships, Department of Medicine, University of Rochester Medical Center, 260 Crittenden Boulevard, Rochester 20, N. Y.

#### EPHRAIM SHORR FELLOWSHIPS IN ENDOCRINOLOGY

The New York Hospital—Cornell Medical Center announces the availability of Junior or Senior Fellowships in Endocrinology and Metabolism. These Fellowships were named for Dr. Ephraim Shorr, who for many years headed this section. Dr. Ralph Peterson, Associate Professor of Medicine, will supervise all Fellowships. Stipends will be between \$5,000 and \$7,500 per year, depending on the number of years following graduation and the number of dependents. The deadline for applications was October 15, 1959.

For further information, please write Dr. E. Hugh Luckey, F.A.C.P., Governor for Eastern New York, Chairman, Department of Medicine, Cornell University Medi-

cal College, 1300 York Avenue, New York 21, N. Y.

#### Personal Notes

Dr. Victor Johnson, F.A.C.P., director of the Mayo Foundation for Medical Education and Research, Rochester, Minn., delivered the Weiskotten Lecture at the 84th annual Alumni Day held June 6, at the State University Upstate Medical Center, Syracuse, N. Y.

Dr. Joseph T. Wearn, F.A.C.P., Dean of Western Reserve University School of Medicine, Cleveland, Ohio, has been appointed to the newly created post of Vice President for medical affairs.

Dr. Lawrence E. Lamb, (Associate), head of the department of internal medicine at the Air Force School of Aviation Medicine, received the Dr. Arnold D. Tuttle award at a meeting of the Aeromedical Association in Los Angeles.

The Home for the Jewish Aged, in cooperation with the Committee on Nutrition and Metabolism of the Philadelphia County Medical Society and the National Vitamin Foundation, are sponsoring a series of lectures on nutrition and metabolism as

they relate to specific medical problems in the aged.

Dr. Robert W. Hillman, F.A.C.P., New York City, will discuss "The Geriatric Patient—Nutritional Requirements," October 11, 1959. Dr. Herbert Pollack, F.A.C.P., New York City, will speak on "General Therapeutic Nutrition with Emphasis on Obesity," November 11. Dr. Richard W. Vilter, F.A.C.P., Cincinnati, will present the topic of "The Relation of Nutrition to Cardiovascular Disease," December 9, 1959.

Dr. Milton J. Steinhardt, (Associate), Detroit, was elected President of the Michigan Allergy Society at the Spring, 1959, meeting of the Society.

Dr. James A. Brussel, F.A.C.P., New York City, whose talents range from psychiatry to crossword puzzles and perfect crimes, has written his first novel, JUST MURDER, DARLING, published by Charles Scribner's Sons, 597 Fifth Avenue, New York 17, N. Y.

The Sloan-Kettering Institute for Cancer Research, the Memorial and James Ewing Hospitals and the Sloan-Kettering Graduate Division of Cornell University Medical College presented a two-week course in cancer chemotherapy October 26 to November 6, 1959. This course included lectures and demonstrations of screening methods, pharmacological technics, methods for the clinical evaluation of potential chemotherapeutic agents and a review of the clinical applications of the functional alkylating agents and miscellaneous other agents in the treatment of cancer.

Dr. Harold L. Goldburgh, F.A.C.P., has been promoted to Clinical Professor of Medicine at the Jefferson Medical College of Philadelphia.

Dr. Edward W. Hayes, Sr., F.A.C.P., Associate Professor of Thoracic Diseases at the College of Medical Evangelists, Los Angeles, received the annual alumni award from the Alumni Association of Carleton College, Northfield, Minn., for distinguished service to the medical profession and devotion to the College. Only 48 persons in the history of the 93-year-old college have received this honor.

Chicagoans, Dr. George C. Turner, F.A.C.P., and Dr. Theodore R. Van Dellen, F.A.C.P., were named President and President-Elect, respectively, of the Chicago Medical Society for 1959-1960.

Dr. Richard S. Ross, (Associate), Baltimore, Md., presented a paper on Pulmonary Hypertension at the Symposium of the Fitkin Memorial Hospital, Neptune, N. J. The General Chairman for this Symposium was Dr. Samuel H. Rubin, F.A.C.P., Director of the Department of Medical Education.

Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, Mich., a Regent of the College, was a guest speaker at the 25th Annual Meeting of the Postgraduate Medical Assembly of South Texas, held in Houston. Dr. Lawrence E. Young, F.A.C.P., Rochester, N. Y., was also a speaker at the Meeting.

Drs. Simon Rodbard, F.A.C.P., James A. Curtin, (Associate), both from the University of Buffalo School of Medicine, and Lawrence E. Young, F.A.C.P., University of Rochester, will be guest speakers in connection with the Visiting Professorship of the Youngstown (Ohio) Hospital Association for the remainder of 1959.

Colonel Leon J. Numainville, F.A.C.P., was recently awarded the Army Commendation Medal with oak leaf cluster for outstanding service during four years at the U. S. Army Hospital, Fort Chaffee, Arkansas, serving as Chief of Medical Service and as Commanding Officer of the Hospital. Colonel Numainville is assigned as Chief of Professional Services, U. S. Army Hospital, Fort Dix, New Jersey.

The Board of Trustees of the American Society of Internal Medicine will meet in Omaha, Nebraska, the weekend of October 31 to plan the program for the fourth annual meeting of the Society which will be held in San Francisco, April 2–3, 1960. In addition to the program, the Board will consider important reports from ASIM Committee Chairmen and explore points of mutual interest with representatives of the National Health Insurance Council. Invited to the meeting also will be representatives of the component societies in the north central region of the United States to hear the latest developments in socio-economic problems as presently viewed by the Officers and Trustees of the American Society.

The President of the American Society of Internal Medicine, Dr. Clark C. Goss, F.A.C.P., has authorized immediate Past President Dr. Elbert L. Persons, F.A.C.P., to have a regional meeting of representatives of component societies during the annual session of the Southern Medical Association in Columbus, Ga., November 16-19. Dr. David E. Hein, (Associate), Secretary-Treasurer of the Georgia Society of Internal Medicine, has been asked to plan the details of this meeting which will be sent to all component societies represented in the Southern Medical Association.

Dr. Stewart P. Seigle, F.A.C.P., President-Elect, and Dr. John R. Williams, Jr., President of the New York State Society of Internal Medicine, represented the American Society of Internal Medicine before the New England Regional Conference of the Committee on Medical Practices of the American Medical Association on July 18 in Boston, Mass. The Regional Conference was for the purpose of developing relative value studies by states represented in the New England area.

Dr. Herbert Berger, F.A.C.P., of Staten Island, N. Y., a member of the Legislative Committee of the American Society of Internal Medicine and President-Elect of the New York State Society of Internal Medicine, represented the national society before the House Ways and Means Committee on July 13. Dr. Berger presented testimony in opposition to the Forand Bill (H-4700) which is also opposed by the American Medical Association.

Drs. George E. Burch, F.A.C.P., New Orleans, and Abe Ravin, F.A.C.P., Denver, were visitors to the 42nd Meeting of the Medical Association of South Africa which was held in East London, Cape Province.

Rear Admiral Edward C. Kenney, (MC), U.S.N., F.A.C.P., has been appointed Deputy and Assistant Chief of the Bureau of Medicine and Surgery.

Rear Admiral Bartholomew W. Hogan, F.A.C.P. and Governor for the College, Surgeon General of the Navy, has been appointed North American Chairman of the Pan American Medical Association's section on military medicine.

Captain Kenneth P. Bachman, (MC), U.S.N., F.A.C.P., has retired after more than sixteen years active service.

Dr. John S. Lawrence, F.A.C.P., Professor and Chairman of the Department of Medicine at the University of California, Los Angeles, has been appointed to the National Arthritis and Metabolic Diseases Council.

Dr. J. Scott Butterworth, F.A.C.P., New York City, has announced that the American Heart Association will begin direct publication of its two scientific journals, *Circulation* and *Circulation Research*, with the January, 1960, number. *Circulation*, issued monthly, is an official journal of the Association and is edited by Dr. Herrman L. Blumgart, F.A.C.P., Boston.

Brigadier General Clement F. St. John, (MC), US.A., F.A.C.P., has assumed command of the Walter Reed Army Medical Center, Washington, D. C.

Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, Pa., President of the American Cancer Society, announced a large scale cancer study which, when in full swing, will study 500,000 families and involve one million persons who are at least thirty years of age. Dr. Pendergrass will also be a featured speaker at the Annual Scientific Session of the Society to be held October 26-27 at the Biltmore Hotel, New York City.

Dr. Norman S. Moore, F.A.C.P., Ithaca, was chosen President-Elect of the Medical Society of the State of New York.

Dr. David A. Cooper, F.A.C.P., Philadelphia, Professor of Medicine, University of Pennsylvania School of Medicine and the Graduate School of Medicine, was presented with the University of North Carolina's distinguished Service Award for 1959.

Dr. C. Sidney Burwell, F.A.C.P., retired as Levine Professor of Medicine, Emeritus, at Harvard Medical School on August 31, after nearly 40 years of active service. At the same time, he retired as physician to the Peter Bent Brigham Hospital and as visiting physician at the Boston Lying-In Hospital.

Dr. Burwell will maintain an office in the Administration Building of the Medical School and will be engaged in writing the history of the Harvard Medical School.

Dr. James M. Faulkner, F.A.C.P., Brookline, Mass., has been elected Chairman of the Joint Administrative Board of the new Boston University-Massachusetts Memorial Hospitals Medical Center. Dr. Faulkner is Director of the Massachusetts Institute of Technology and Professor of Clinical Medicine at the Boston University School of Medicine.

Dr. Harry E. Ungerleider, F.A.C.P., New York, has been appointed as a Consulting Medical Director of the North American Reassurance Company.

Dr. Robert G. Heath, F.A.C.P., Professor and Chairman of the Department of Psychiatry and Neurology, Tulane University School of Medicine, was elected President-Elect of the New Orleans Society of Neurology and Psychiatry.

Dr. Henry McIntosh, (Associate), Durham, has been elected President-Elect of the North Carolina Heart Association. Dr. Charles G. Sawyer, (Associate), Winston-Salem, was chosen Vice President.

Dr. Charles H. Burnett, F.A.C.P., Professor and Head of the Department of Medicine, University of North Carolina School of Medicine, has been elected a member of the American Academy of Arts and Sciences.

Dr. Milford O. Rouse, F.A.C.P., Dallas, Texas, President of the Southern Medical Association, was elected Vice-Speaker of the House of Delegates of the American Medical Association.

Dr. May Owen, F.A.C.P., Forth Worth, Texas, will become the first woman President of the Texas Medical Association in 1960. The only other woman physician ever to be accorded a similar honor was Dr. Leslie S. Kent, who was President of the Oregon State Medical Society in 1948.

Dr. Jackson A. Smith, F.A.C.P., has recently accepted an appointment as Clinical Director of the Illinois State Psychiatric Hospital, Chicago. Dr. Smith was formerly with the Nebraska Psychiatric Institute, Omaha.

Captain Cecil L. Andrews, Medical Corps, U. S. Navy, F.A.C.P., Commanding Officer of the U. S. Naval Hospital, St. Albans, N. Y., has been selected for promotion to the rank of Rear Admiral.

Colonel Frank M. Townsend, Medical Corps, U. S. Air Force, F.A.C.P., has been appointed Director of the Armed Forces Institute of Pathology. Colonel Townsend is the first Air Force Officer to assume the Directorship of the Institute.

Dr. Jacob M. Ravid, F.A.C.P., F.C.A.P., New York, Pathologist and Director of Laboratories, St. Clare's Hospital, read a paper, "Malignant Melanoma of the Nose and Paranasal Sinuses and Juvenile Melanoma of the Nose," before the Section on Laryngology, Otology and Rhinology at the 108th Annual Convention of the American Medical Association in June.

Dr. Walter S. Thompson, Jr., F.A.C.P., Baldwin Hills, was elected President of the Los Angeles County Heart Association. Dr. Willard Zinn, (Associate), Los Angeles, was elected Director of the Cardiac Resuscitation Committee and Dr. Mitchel D. Covel, (Associate), Beverly Hills, was elected Medical Director of the Program Committee for Research.

Dr. Bernard S. Lipman, F.A.C.P., Atlanta, Ga., returned recently from Minneapolis where he was a guest lecturer for a postgraduate course in electrocardiography given by the University of Minnesota Center for Continuation Study.

## **OBITUARIES**



WILLIAM D. STROUD, M.D., F.A.C.P., Philadelphia, Pa. Treasurer (1932-1958), American College of Physicians

## DR. WILLIAM DANIEL STROUD

Dr. William Daniel Stroud, a distinguished Fellow of the College, died August 19, 1959, in the Bryn Mawr Hospital following a long illness.

Born in Villanova, Pennsylvania, November 20, 1891, he attended the Haverford School and the University of Pennsylvania, receiving the degrees of B.S. in 1913, and M.D. in 1916. He served his internship in the Pennsylvania Hospital, Philadelphia. During the years 1918–19 he served on the Cardiovascular Board, General Hospital 9, Lakewood, New Jersey. From 1919–20 he pursued postgraduate study under Sir Thomas Lewis in the University College Hospital, London; Sir James MacKenzie in St. Andrew's Institute for Clinical Research, and in l'Hospital de Pitié, Paris.

His achievements in teaching and practice, and his participation in the work of various organizations were outstanding. Throughout most of his professional life he served on the staffs of the Graduate Hospital, the Pennsylvania Hospital, and the Children's Heart Hospital, Philadelphia, and the Bryn Mawr Hospital. His academic titles included: Professor of Cardiology, Graduate School of Medicine and Assistant Professor of Clinical Medicine, School of Medicine, University of Pennsylvania. He served as Consulting Cardiologist to other institutions in the Philadelphia area, including the Abington Memorial, St. Christopher's, Montgomery, and the Norristown State Hospitals, and the Children's Seashore House.

Following his election to Fellowship in the American College of Physicians in 1930 he served as Treasurer from 1932 to 1958, was a Member of the Board of Regents and of the Executive Committee and of other committees, and received the Alfred Stengel Memorial Award in 1957. It can truly be said that his was a most important contribution to the growth and development of the College.

Other organizations which he served included The Philadelphia Heart Association (Secretary); The American Heart Association (President); The American Clinical and Climatological Association; The Interurban Clinical Club; The College of Physicians of Philadelphia; The Association of American Physicians; The Philadelphia Tuberculosis and Health Association (Board of Directors); The National Medical Advisory Board of the National Rehabilitation Commission of the American Legion; a Member of the Research Advisory Committee on Problems of Aging, Veterans Administration; The Committee on Cardiovascular Diseases of the National Research Council; and Honorary Member of the Brazilian Society of Cardiology and the Philippine Heart Association.

During his lifetime he prepared numerous scientific papers in the field of heart disease, and was editor of *The Diagnosis and Treatment of Cardiovascular Diseases*, published in 1940. He was a man of great personal friendliness and charm, exhibiting warmth which was readily felt by patients and colleagues alike. His talents were large, his life was most productive. His friends throughout the world feel a keen sense of loss at this time.

Surviving are his wife, Agnes H. Stroud, 1717 County Line Road, Villanova, Pennsylvania; a son, Samuel Stroud, of Newport, Rhode Island; and three daughters, Mrs. Agnes Ball, Mrs. Charlotte Ingersoll, and Mrs. Margaret Arndt.

WILLIAM A. JEFFERS, M.D., F.A.C.P. Governor for Eastern Pennsylvania

## DR. GEORGE HOWARD HOXIE

The College regrets the death of Dr. George Howard Hoxie, F.A.C.P., in Berkeley, Cal., on April 10, 1959.

Dr. Hoxie was born July 24, 1872, in South Easton, N. Y. He received his A.B. and A.M. degrees from Union College, Schenectady, N. Y., in 1893 and 1896, respectively. He attended the University of Zurich, from which institution he received his M.D. in 1901. In 1904 he did postgraduate work in hematology at Columbia University.

Dr. Hoxie then moved to Kansas City, Mo. where he was very active in civic affairs. He was a member of the staffs of Kansas City General, Research, and St. Luke's Hospitals. During the years 1902 to 1905 he was Medical Director of Public Schools. He was Associate Professor of Anatomy at the University of Kansas City School of Medicine, and in 1905 to 1911 was Professor of Medicine at the same institution. He later became Dean of the Clinical Department.

He was a member of the American Medical Association and Association for the Study of Internal Secretions, having been Director of the latter for many years. He was a member of the Missouri Medical Association, the Jackson County (Mo.) Medical Society, American Therapeutic and the American Tuberculosis Societies. He belonged to the Association of American Medical Colleges (President of this organization in 1908) and Missouri Tuberculosis Association, having served as President one term.

Dr. Hoxie, a Diplomate of the American Board of Internal Medicine, was practically a "founder" member of the American College of Physicians, having become a Fellow in 1919.

In his later years he took up residence in Berkeley, Cal. where he led a full life. He is survived by his wife, Ida Shaker Hoxie.

STACY R. METTIER, M.D., Governor, Northern California and Nevada

#### DR. ROBERT FRANKLIN IVES

Dr. Robert Franklin Ives was born March 21, 1870, Brooklyn, New York, and died June 30, 1959 in Houston, Texas. He received his undergraduate education at Cornell University, and his medical degree at Columbia University College of Physicians and Surgeons, 1895. From 1895 to 1896 he interned at Newark City Hospital, Newark, New Jersey.

Dr. Ives specialized in diseases of the heart and arteries. He worked under Professor Schlesinger in Vienna, Austria, under Dr. Mackenzie at the London Hospital in England, and with Sir Thomas Lewis at the University Hospital in London,

England.

Dr. Ives was elected a Fellow in the American College of Physicians in 1917, and was, therefore, one of the early members of the College. In addition to his membership in the College, Dr. Ives was a Fellow of the New York Academy of Medicine, a Fellow in the American Society of Internal Medicine, a member of the American Medical Association, Brooklyn Society of Internal Medicine, Brooklyn Medical Association, Brooklyn Pathological Society, Medical Society of the Greater City of New York, Associated Physicians of Long Island, Flatbush Medical Society and Medical Society of the State of New York. He was also a Diplomate of the American Board of Internal Medicine.

Many of Dr. Ives' articles appeared in leading state and national medical journals. Dr. Ives is survived by his son, Dr. Robert M. Ives, Houston, Texas. His confreres note with sincere regret the passing of Dr. Ives.

E. HUGH LUCKEY, M.D., Governor for Eastern New York

#### DR. CHARLES HOWARD MINER

Dr. Charles Howard Miner, F.A.C.P., former Secretary of Health, State of Pennsylvania, died July 12, 1959. Dr. Miner had been confined to his home for several months with a succession of illnesses. He was born in Wilkes-Barre, Pa., July 5, 1868. He received his B.S. degree from Princeton in 1890 and his doctor of medicine degree from the University of Pennsylvania in 1893. For eighteen months he was an intern in the Presbyterian and Children's Hospital in Philadelphia.

In 1895 Dr. Miner went to Europe for postgraduate study at Heidelberg and Vienna. Returning to Wilkes-Barre in 1896, he thereafter practiced internal medicine, interrupting this practice in 1927 to pursue postgraduate study in cardiology at the University of Pennsylvania. He was the first practicing cardiologist in Wyoming Valley.

Among Dr. Miner's interests was the field of public health. One of his chief contributions in this was his successful effort in founding the Wyoming Valley Tuberculosis Society 53 years ago. He served as its president from that time until 1948. He served also as President of the Pennsylvania State Tuberculosis Association. Also, he aided in planning the Kirby Health Center in Wilkes-Barre and was President of the board of this Health Center in 1943.

In recognition of Dr. Miner's long and active career in the health field and leadership in the fight against tuberculosis, the Hamburg Tuberculosis Sanitarium, Berks County, Pa., was renamed the Charles H. Miner State Hospital in 1956.

Dr. Miner was a member of the Luzerne County Medical Society, becoming its President in 1910, a member of the Pennsylvania State Society, American Medical Association, Pennsylvania Tuberculosis Society, Pennsylvania and American Heart Associations, American Clinical and Climatological Society and had been a Fellow of the American College of Physicians since 1923. Also, he was a Fellow of the College of Physicians of Philadelphia and a Diplomate of the American Board of Internal Medicine.

Dr. Miner will be greatly missed by his wide circle of friends and admirers. Surviving are his wife, a son, Attorney Charles H. Miner, Jr., Kingston, Pa., a daughter, Miss Stella Miner, at home, and two granddaughters.

HOWARD Y. HARRIS, M.D., F.A.C.P.

#### CAPTAIN FRANKLIN F. MURDOCH

Captain Franklin F. Murdoch, Medical Corps, U. S. Navy (retired), died at his home in Bremerton, Washington, April 3, 1959. He was 69.

Born in Brooklyn, New York, September 8, 1889, he was a 1911 graduate from the New York Homeopathic Medical School, New York City, from where he received the degree of Doctor of Medicine. He was commissioned Lieutenant (junior grade) in the Medical Corps of the Navy February 5, 1917, and through subsequent promotions attained the grade of Captain, with date of rank July 1, 1940.

During his forty years of active naval service, Captain Murdoch served with the Medical Department of the Navy throughout the United States and abroad, and in ships of the fleet. Former assignments included: Executive Officer, U. S. Naval Hospital, Bremerton, Washington; Commanding Officer, U. S. Naval Hospital, Seattle, Washington (from 1939 to 1942); and Commanding Officer of Mobile Hospital No. 3 and Base Hospital No. 11 in the South and Southwest Pacific (1943–1944). He was retired from active service January 1, 1947.

Captain Murdoch was a Diplomate of the American Board of Internal Medicine, and a Fellow, American College of Physicians since 1926.

He is survived by his wife, Bernice, of Bremerton, Washington.

Rear Admiral Bartholomew W. Hogan, M.D., Governor for U. S. Navy

## DR. ALFRED WILLIAM PENNINGTON

Alfred William Pennington, M.D., F.A.C.P., internist for the Engineering Department of the DuPont Company, died at his home in Newark, Del., on August 9, 1959.

Dr. Pennington was born in Newark, N. J., April 9, 1903. He received his B.A. degree from Wake Forest College in 1924 and the degree of doctor of medicine from the Medical College of Virginia in 1929. He served his internship at St. Barnabas Hospital, Newark, N. J., and furthered his postgraduate training in cardiovascular disease at the New York Post-Graduate Hospital and Medical School, and at the Mt. Sinai Hospital, New York City. From 1944 to 1948 he served as attending physician at New York University, Bellevue Hospital and Cardiac Clinic while engaged in private practice in Essex County, N. J.

He was a Diplomate of the American Board of Internal Medicine and the American Board of Preventive Medicine. He was elected an Associate of the College in 1950 and became a Fellow in 1958.

Dr. Pennington was widely known for his contributions to medical literature on nutrition, and was particularly interested in obesity.

He is survived by his wife, Mrs. Evelyn Williams Pennington, and a son,

Anthony J. Pennington, of Ann Arbor, Michigan.

Dr. Pennington maintained an active interest in the affairs of the College and attended Annual and Regional meetings regularly. His presence and helpful influence will be missed.

> WARD W. BRIGGS, M.D., F.A.C.P., Governor for Delaware

## DR. CORNELIUS P. RHOADS

Dr. Cornelius Packard Rhoads, Director of the Sloan-Kettering Institute for Cancer Research since its founding in 1945, was born in Springfield, Massachusetts on June 20, 1898 and died suddenly of a heart attack on August 13, 1959 at his home in Stonington, Connecticut.

Dr. Rhoads received a Bachelor of Arts degree from Bowdoin College in Brunswick, Maine, and was graduated cum laude with a Medical Degree from the Harvard Medical School in 1924. He received an honorary Doctor of Science degree from Bowdoin College in 1944, an honorary Doctor of Science degree from Williams College in 1952 and an honorary Doctor of Laws degree from the University of Saskatchewan in 1958.

Dr. Rhoads served his internship in the Department of Surgery at the Peter Bent Brigham Hospital in Boston in 1924-1925. Following this he was a Trudeau Fellow at Trudeau Sanatorium in Saranac Lake, New York, in 1925-26. He was an Instructor in Pathology at the Harvard Medical School and Assistant Pathologist at Boston City Hospital in 1926-1928. In 1928 he joined the staff of the Rockefeller Institute for Medical Research in New York. He served there as an Associate, Pathologist and Associate Member before his appointment to Memorial Hospital in 1939

During World War II Dr. Rhoads served as Chief of the Medical Division of the Army's Chemical Warfare Service for which he received the Legion of Merit.

He was named Professor of Pathology at the Cornell University Medical College in 1940, and held that post until 1952 when the Sloan-Kettering Division of Cornell University Medical College was created. At that time Dr. Rhoads, the Director of the Sloan-Kettering Institute, became Professor of Pathology in the Division's Department of Biology and Growth, a post he held at the time of his death.

Dr. Rhoads was a Fellow in the New York Academy of Medicine and had served on its Committee on Public Health Relations. He was a Vice President of the Academy from 1943-45.

He was a member of the National Research Council and, during World War II, served as a member of its Sub-Committee on Blood Substitutes, as a member of its Committee on Veterans' Medical Problems, as a member of its Committee on Atomic Casualties and as Chairman of its Committee on Growth. Later in the 1940's he became a Member of the Council's Advisory Committee on Chemical-Biological Coordination Center and a Member-at-large of its Division of Medical Sciences.

Dr. Rhoads held memberships in the American Association for Cancer Research, American Association of Pathologists and Bacteriologists, American Geriatrics Society, American Industrial Hygiene Association, American Medical Association, American Public Health Association, American Radium Society, American Society for Clinical Investigation, American Society for Experimental Pathology, American Cancer Society, American Society for the Prevention of Cruelty to Animals, American Society of Tropical Medicine, Association of American Physicians, Medical Society of the State of New York, James Ewing Society, Inter-Society Cytology Council (Founder Membership), and many others indicating his wide interests and vigor.

Dr. Rhoads' publications of work in pathology and cancer research have appeared in most of our leading scientific journals. As a member of the American College of Physicians he was active in the scientific programs of the annual meetings and a loyal contributor to many of the postgraduate courses.

Dr. Rhoads is survived by his wife, Katherine Southwick Bolman Rhoads. His colleagues note with deep regret the passing of Dr. Rhoads.

E. HUGH LUCKEY, M.D., Governor for Eastern New York

## DR. SIDNEY ALEXANDER SLATER

Dr. Sidney Slater, F.A.C.P., was born at Enfield, Virginia, on August 26, 1884, and died on June 12, 1959.

Dr. Slater attended Richmond College (now Richmond University) and in 1905 received the degree of Bachelor of Arts. He then attended the University of Virginia College of Medicine and in 1909 received the degree of Doctor of Medicine. After graduating from medical school he served an internship in Richmond City Hospital after which he immediately entered general practice at McComas, West Virginia. In 1912 he became a victim of clinical tuberculosis as did so many students and recent graduates of medicine in those years. When he had recovered sufficiently he went to Grand View Sanatorium, Oil City, Pennsylvania, as Medical Director and served in that capacity until 1919. Dr. Slater became widely known for his expertness in tuberculosis and in January, 1919, he assumed the duties of a new position as Medical Director of the Southwestern Minnesota Sanatorium at Worthington. Dr. Slater served in this capacity until his retirement in 1957 at which time this institution was closed. With retirement at the sanatorium, Dr. Slater established a private practice in Worthington where he and his wife Mildred resided

Although he brought under control the clinical pulmonary tuberculosis of which he was first aware in 1912 its residuals continued to harass him. Approximately 25 years ago tuberculosis developed in his left elbow to such an extent that he was compelled to wear a cast for the remainder of his life. Emphysema resulted in serious reduction of pulmonary function in the last few years.

Dr. Slater was a member of the American Medical Association, the American Sanatorium Association, the Minnesota State Medical Society, the Southern Minnesota Medical Society, the Trudeau Medical Society of Minnesota, and a Fellow in the American College of Physicians.

Since 1913, when he first became medical director of a sanatorium, his life was devoted wholeheartedly to the diagnosis, treatment, and prevention of tuberculosis. Few physicians have lived who have so completely comprehended tuberculosis in all of its aspects as did Dr. Slater. Few have diagnosed so accurately, treated so successfully, and prevented so effectively.

Hugh R. Butt, M.D., F.A.C.P., Governor for Minnesota

### DR. THOMAS H. A. STITES

His colleagues note with sorrow the passing of Dr. Stites on May 23, 1959, following a stroke, at his home R. D. 3, Nazareth, Pennsylvania.

Dr. Sites was born April 26, 1875, in Wyoming, Pennsylvania. He graduated from Princeton in 1896, and from the University of Pennsylvania, School of Medicine, in 1901.

His professional life was divided between hospital administration and contributions to various medical organizations: From 1907 to 1914 he was Medical Inspector of Dispensaries, Pennsylvania Department of Health. He served as Medical Director, Hamburg (Pa.) State Sanitorium from 1914 to 1920. Other assignments included directorships of U. S. Public Health Service Hospital No. 29, Alexandria, Virginia, and the State Tuberculosis Sanatorium, Cresson, Pennsylvania.

He was a Fellow of the American Trudeau Society. He held offices in the Medical Society of the State of Pennsylvania and the Northampton County (Pa.) Medical Society. Elected to Fellowship in the American College of Physicians in 1931, he became a life member in 1941.

His many friends in the College share the loss felt by Mrs. Stites.

WILLIAM A. JEFFERS, M.D., F.A.C.P., Governor for Eastern Pennsylvania

## DR. GEORGE FRANKLIN STONEY

Dr. George Franklin Stoney, F.A.C.P., of Erie, Pa., died February 1, 1959. The cause of death is unlisted.

Dr. Stoney was born May 4, 1886, in Cleveland, Ohio, and received his M.D. degree from Jefferson Medical College of Philadelphia in 1910. Thereafter, he did postgraduate work at Harvard Medical School and at Columbia University College of Physicians and Surgeons. He also had graduate training at the Philadelphia General Hospital.

He was Head of the Diabetic Clinic and Consultant in Medicine at Hamat Hospital in Erie. Dr. Stoney's chief interest in the field of internal medicine was in metabolic diseases, particularly diabetes mellitus. For several years he was quite active as a member of the Commission on Diabetes of the Pennsylvania State Medical Society.

Dr. Stoney was a member of the American Medical Association, the Medical Society of the State of Pennsylvania, the Erie County Medical Society, a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1931. He became a Life Member in 1944. Dr. Stoney displayed an abiding and loyal interest in the College and seldom missed attending its Annual Sessions and Regional Meetings. His judgment was sound; his friendship, enduring.

Dr. Stoney is survived by his wife, Mrs. Blanche J. Stoney, of Roslindale Avenue, Erie, Pa.

FRANK J. GREGG, M.D., F.A.C.P., Governor for Western Pennsylvania

#### THE AMERICAN COLLEGE OF PHYSICIANS

IMPORTANT TRANSACTIONS OF BOARD OF REGENTS AND BOARD OF GOVERNORS

Board of Regents, April 18, 1959, Chicago:

RESOLVED, that the Executive Committee of the Board of Regents and the Committee on Administrative Personnel be authorized to select specific nominees for the position of Executive Director and that of an Assistant Executive Director and report to the Board of Regents at its November, 1959, meeting, or prior thereto as occasion dictates; elections shall be formally made by the Board of Regents as a whole.

RESOLVED, that it is the opinion of the Board of Regents that any financial difficulties of the American Society of Internal Medicine might be readily alleviated through the receipt of adequate dues from additional members; that some form of suitable publicity, acceptable to the Editor of the Annals of Internal Medicine, may be published to encourage Fellows and Associates of the College to join the American Society of Internal Medicine, which would in no way commit the College to any form of underwriting.

RESOLVED, that the A.C.P. Liaison Committee accept the invitation to be represented at Council meetings of the American Society of Internal Medicine, expenses of A.C.P. members to be borne by the College.

RESOLVED, that the College authorize the publication in the Annals of Internal Medicine of the lists of Presidents and Secretaries of the A.S.I.M. component societies.

RESOLVED, that the term of office presently specified as two years for the A.C.P. Liaison Committee with the A.S.I.M. be changed to three years.

RESOLVED, that the Board of Regents, anticipating continuation of the Study of Paramedical Areas in Relation to Medicine, change the status of Dr. Edward C. Rosenow, Jr., from observer to official representative of the American College of Physicians.

RESOLVED, that the Board of Regents approve and execute the necessary resolutions required of depositories of the College in connection with the Royal Bank of Canada, the Girard Trust Corn Exchange Bank and the Provident Tradesmens Bank and Trust Company.

RESOLVED, that the Chairman of the A.C.P. Committee on Finance and Budgets shall be authorized to sign checks against the College accounts in the absence or incapacitation of the Treasurer.

RESOLVED, that the Philadelphia Saving Fund Society be designated as official depository for saving fund deposits.

RESOLVED, that the Board of Regents approves the suggestion of the College bonding agent for a single bond covering the Treasurer, the Executive Secretary, and any other employees that should be bonded.

RESOLVED, that the Chairman of the Committee on Finance and Budgets shall be bonded in the amount of \$50,000.00, premium to be paid by the College.

RESOLVED, that the Board of Regents approves of the exploration of the establishment of a post of public and professional relations and the establishment of the functions of such post; also the exploration of a qualified individual for appointment to such post.

237 candidates were elected to Associateship and 212 candidates were elected to Fellowship; 37 Associates were dropped from the roster due to failure to qualify for advancement to Fellowship in the maximal ten-year period.

RESOLVED, that a Committee on Publications be appointed as a standing committee of the College, to replace the present Editorial Board of the Annals of Internal Medicine as presently constituted; that the Committee on Publications be enlarged to seven members, with the majority Regents of the College.

RESOLVED, that there be a specific Editorial Board of the Annals of Internal Medicine, this board to be selected by the Editor, subject to the approval of the Committee on Publications and thereafter approved by the Board of Regents; that the Chairman of the Committee on Publications shall be a member ex officio of this new Editorial Board.

RESOLVED, that the Editor of the Annals of Internal Medicine, who will eventually succeed Dr. Maurice C. Pincoffs, shall be appointed independently and solely for potential or proved editorial ability, and shall not be a part of the executive or administrative office of the College.

RESOLVED, that Dr. Thomas M. McMillan, of Philadelphia, shall be elected Editor of the Bulletin of the American College of Physicians; that the Editor of the Bulletin shall be an ex officio member of the Committee on Publications.

It was recorded that the Editor of the Bulletin and the Editor of the Annals should work in close coöperation with one or more of the administrative officers, but that each should be in the position of being independent and should not be dependent upon the administrative office, except so far as the business administration of the two publications is concerned.

RESOLVED, that the American College of Physicians shall add its endorsement to the proposal of the Pharmaceutical Manufacturers Association, with regard to the establishment of a new National Council for the Advancement of Medical Research and Education.

The resignations of one Fellow and seven Associates were accepted; one Associate was dropped from the roster because of delinquency in dues for a period of more than two years.

It was revealed that the share of the American College of Physicians in support of the Joint Commission on Accreditation of Hospitals, general operations, was \$18,897.00, and for surveyors' employment and expenses, \$28,702.17.

It was recorded that the College had again been elected to the National Research Council, Division of Medical Sciences, from 1959 to 1962, and that its official representative, Dr. Chester S. Keefer, had been reelected to the Executive Committee of the Division of the Council.

RESOLVED, that in accordance with the recommendations of Dr. Richard A. Kern, who had previously been appointed to prepare a Manual of Rules, Policies and Procedures, that in regulations governing committees, it should be prescribed, referring to Chairmen's reports, "his report may be verbal, but must be supplemented by each committee report in writing for inclusion in full in the Minutes of the Board of Regents and for distribution to all Regents. All Chairmen of committees, if they so request, shall receive the privilege of the floor in discussion when the Board of Regents takes action based on their committee reports." This provision was intended to take care of so-called subcommittee reports made through master committees and often resulting in no adequate or specific report reaching the Board of Regents.

## Board of Governors, April 19, 1959, Chicago:

Announcement: Major General Leonard D. Heaton, as of May 1, 1959, would become Surgeon General of the U. S. Army and College Governor for the Army.

RESOLVED, that in view of the reduced number of doctors applying for American Board of Internal Medicine examinations, in view of the high rate of failures reported in the examinations, and in view of the interest of the American College of Physicians in Board certification, the Board of Governors respectfully requests a critical analysis of bases for failures and successes, with a view to presenting results of this analysis to the next annual meeting of the Board of Governors.

RESOLVED, that an initial survey made by a special committee on investigation of Governors' expenses be accepted as informational, and that the committee be continued, to report back to the Executive Committee of the Board of Governors in November, 1959.

The Governors received a report from the Executive Secretary revealing 31 Regional Meetings had been held since the previous Annual Session; membership participation, 2,500; non-member participation, 1,437; grand total attendance, 3,937; a 20% increase in the number of meetings, with a proportionate increase in attendance over the previous year.

Report of the Committee on Postgraduate Courses revealed 8 courses given during the autumn-winter 1958-59, with total registration of 903; 654 A.C.P. members; 249 non-members (compared with the autumn-winter 1957-58, this was an increase of 243 registrants). Many courses had been oversubscribed; titles and schedules of current and future courses were recorded and their publication approved and authorized. The Committee recommended that matriculation fees be increased from \$30.00 to \$60.00 for A.C.P. members; from \$60.00 to \$80.00 for non-members, this based on providing adequate funds for the expenses of directors and the overhead of the College.

Dr. Sven M. Gundersen, Hanover, N. H., was elected a member of the Committee on Credentials representing the Board of Governors, to fill the unexpired term of Dr. Richard P. Stetson, resigned. Dr. Marshall N. Fulton, Providence, R. I., was elected Chairman of the Board of Governors; Dr. George C. Griffith, Los Angeles, Calif., reëlected Vice Chairman; Dr. Theodore J. Abernethy, Washington, D. C., and Dr. Wright Adams, Chicago, Ill., were elected members of the Executive Committee of the Board of Governors, to fill vacancies of Dr. Irving S. Wright and Dr. Charles M. Caravati, who were retiring from the Board of Governors. Dr. John C. Leonard, Hartford, Conn., and Dr. Frederick W. Madison, Milwaukee, Wis., were elected to the Executive Committee of the Board of Governors to fill out unexpired terms of Dr. Carl V. Moore (1960) and Dr. Marshall N. Fulton (1960), respectively.

WHEREAS, Mr. Edward R. Loveland, our beloved Executive Secretary, will retire from active participation in the affairs of the American College of Physicians on December 31, 1959, and therefore will no longer be available to us as our administrator, now

"THEREFORE BE IT RESOLVED, that it is the considered opinion of the Board of Governors that his administrative leadership and indefatigable efforts are largely responsible for the remarkable growth and continued prestige of the College, and that each member of this Board trusts that his years of retirement will be filled with much happiness, satisfaction and good health, and that the Board does now officially express to him its sincere thanks for his long, efficient and devoted service to the College and for his many acts of kindness to each of us."

Joint Executive Session, Board of Regents and Board of Governors, April 19, 1959, Chicago:

"President's Review of A.C.P. Activities of the Past Year (Dr. Dwight L. Wilbur)

"Last fall the College was faced with the sudden and unexpected illness of Mr. Loveland. You can see from his presence here today that his recovery has been quite satisfactory. I assure you that he has been putting in very long days for a long time now in the interest of this Session and of the College.

"The most important decision made by the Board of Regents last November had to do with the decision to find a successor as the Chief Administrative Officer

of the College—a physician, an internist, a Fellow of the College, an individual who would take over at such time as Mr. Loveland may retire, December 31, 1959. The title of the new appointment will be Executive Director.

"In the contemplated reorganization of the administrative setup of the College, there will also be an Assistant Executive Director who will be a layman, and then such other assistants as are needed to carry out the professional public relations, educational and business activities of the College.

"Mr. Lewis Lang was appointed on December 1, 1958, as Assistant Executive Secretary who among other duties has those of the public relations of the College.

"I should also point out that the changes in administration are going to cost the College more money than has been expended in the past for administration. However, with the growth of the College and of its activities, these administrative changes are inevitable and will have to be faced by the College.

"So far as the organizational structure and function of the College are concerned, there have been a number of changes effective either during this past year or contemplated in the future. The first of these has to do with the new Constitution and By-Laws, which has been under study by the Board of Regents for some three years and about which you will hear more subsequently.

"The Regents have also established certain regulations, primarily in respect to committee structure and function, so that these are now spelled out and can be clearly understood by members of the Committees and of the Board of Regents.

"Finally, at the suggestion of past President Richard A. Kern, there will be established a 'Manual of Rules, Policies and Procedures' of the College, so that this will simplify the administrative understanding of the functions of the College and, for those who come along in the future, will be the mechanism of function in regard to College activities. In respect to the functioning of Committees, there has been an effort to streamline the functions of Committees of the College, to the end that the Board of Regents can function more effectively and the members be better informed. We have established now some eight major Committees; none of them new—Executive Committee, Committee on Credentials, Committee on Educational Program, Committee on Finance and Budgets, Committee on Awards, Committee on Masterships and Honorary Fellowships, Committee on Nominations and the Governors' Executive Committee—then, also, we have established other Committees as subcommittees of these major Committees, to report to them and then the parent Committees shall report to the Board of Regents.

"This past November was the first time in which this new Committee setup had a chance to operate. It did not function as smoothly, I am sure, as all of us hoped, but at least it saved the Board considerable time and permitted it to consider more carefully many important matters which in the past had to be rushed through in order to conclude the business by the time of the established adjournment.

"Several Committees during this past year have essentially completed their tasks. First of these is the Committee on Pensions, which has established a very sound system of pensions for the College. The Committee remains as a standing committee, but its work is essentially finished until some problem may arise. The Committee on Awards Structure has for a number of years been carefully reviewing this complicated problem, and with the exception of two or three minor points now has satisfactorily established the awards structure of the College, so as to greatly simplify it. The Committee on Administrative Structure has completed its task and was discharged last November. New Committees consist of the Committee on Administrative Personnel, which is carefully looking into the matter of the members of the top administrative staff, A Committee to Study the Selection of Annual Session Sites has been appointed, with the duty of reviewing in detail the facilities of various cities and to pass on to the Board of Regents their recommendations.

"Upon the recommendation of the Board of Regents, Dr. Richard A. Kern has

been appointed as a representative of the College on the Joint Commission on Accreditation of Hospitals.

"In respect to publications of the College, there has been established the Bulletin of the American College of Physicians. This Bulletin, which will first appear next February, will incorporate the present News Notes of the College now appearing in the Annals, along with other material selected for publication. This will not only relieve the Annals of carrying material which is now taking the place of scientific material, but will also give the College a vehicle by which it can present to its members the important actions of Boards, such as the Regents and Governors, and of Committees, and other information which is important to the members of the College.

"The Annals of Internal Medicine faces a crisis, because its Editor, Dr. Maurice C. Pincoffs, has indicated that by August, 1960, he would like to retire. This, naturally, produces for our Editorial Board a considerable problem in finding someone who can handle this important position.

"In respect to the scientific program of the Annual Session, the important changes had to do with two things—first, the holding of two simultaneous Clinical Sessions, which are, in part, categorized, and, second, the addition of outstanding programs in Basic Medical Sciences and in Clinical Investigation. These features, which have been the work of the Committee on Program, have occasioned very favorable comment as I have passed around the country, and I hope very much that the way in which they are attended and the manner in which they are carried out will insure that they become part of the program of the College in the future.

"One weak point in our scientific program are the Scientific Exhibits. I think this matter should be carefully studied and perhaps abandoned for the time being, because the exhibits are really not up to the standards of the remaining part of the program.

"In respect to professional and public relations, there will be held at this meeting an Invitation Session for some two hundred executives of the Chicago area. This is a new departure for the College. I hope its execution is good. So far the reactions have been very favorable, not only from the individuals invited, but also from those of the press, television and radio who are very responsive to the actions of medical organizations such as this. This is clearly within the objects as stated in the Constitution, to keep the public informed as to what is going on in the field of Internal Medicine by internists. This appears to be an important obligation of the College.

"You will hear more in detail later as to some of the professional relations that are being contemplated.

"The Liaison Committee of the College with the American Society of Internal Medicine continues to bear a very close relationship. I suspect there will continue to be a relationship for some time, because while our interest in the College is primarily in matters related to education, to high standards and progress of the profession, these interests are really inseparable from the socio-economic problems in which the ASIM is primarily interested.

"In respect to new business, you will hear later on about the new Professional Liability coverage which the College is now carrying with the Liberty Mutual Insurance Company of Boston.

"After the meeting of the Board of Regents last November, the College filed in Appellate Court of California a brief as a friend of the Court in the Cutter Laboratories' case, in which the legal principle of implied warranty was brought up. I should say parenthetically that if this court decision stands, then the principle of implied warranty will apply almost certainly to some and perhaps all biological products. Therefore, the Board of Regents felt that this was a very important matter and that it should file this brief as a friend of the court, urging the Appellate Court to reverse the decision of the lower court. It will probably be another five

or six months before a decision is rendered. It is quite likely that whatever decision is made, it may be appealed to the Supreme Court of the State of California.

"The growth of the College continues, and up to yesterday 10,386 members were in the College.

"Reviewing briefly the actions of the Board of Regents yesterday, a Committee on Publications was established as a standing committee of the Board of Regents, said committee to be composed of seven to nine members, the majority of whom shall be Regents. It was also established that there shall be an Editorial Board of the Annals of Internal Medicine to assist the Editor with his editorial duties, this Board to be selected by the Editor, with approval of the Committee on Publications and of the Board of Regents. Term of members of the Editorial Board shall be limited to two terms of three years each, with a possibility of one additional three-year appointment after a lapse of one year, the original members to be appointed for periods of one, two and three years, in order to create a standard rotation.

"The Chairman of the Committee on Publications shall be a member ex officio of the Editorial Board. Any future Editor of the Annals is to be appointed independently and solely for editorial ability, and he shall not be a part of the executive or administrative setup of the College.

"Dr. Thomas M. McMillan, of Philadelphia, was confirmed as Editor of the new Bulletin, for a term of three years. It is provided that the Editor of the Bulletin shall be an ex officio member of the Committee on Publications.

"A resolution to the effect that 'The American College of Physicians commends the National Voluntary Health Agencies and expresses its confidence in their leadership program and policies, particularly their influence in furthering major advances in scientific research and medical knowledge and the vital role they are playing in the advancement of the nation's health, which is the basic interest of the medical profession,' was not adopted.

"The Regents also considered a communication from the Pharmaceutical Manufacturers Association, regarding the establishment of a new National Council for the Advancement of Medical Research and Education, based on the Bayne-Jones report. The principle was endorsed by formal resolution of the Regents.

"Finally, the Board of Regents was apprised of a communication from Dr. Arthur R. Colwell, Chairman of the Committee on Standards of Hospital Practice in Internal Medicine, which included a proposal for the release of popularized reports about their problems and the efforts made to solve them, these to be designated for the medical press generally and to take the form of news reports and occasional special stories for medical consumption. By resolution, the Board of Regents approved the recommendation of Dr. Colwell's Committee."

#### "Report, Committee on Insurance

Dr. Joseph D. McCarthy, Chairman, gave a brief summary report on the current status of the various insurance plans sponsored by the College.

	Accident & Health	Malpractice	Specified Disease
Total number of certificates issued	5,264	2,960	2,922
Less: certificates not in force	631	716	190
Total number of certificates currently in force	4,633	2,244	2,732
Number of Claims received	2,576	136	59
Total amount of claim payments to date	\$1,535,925.15	\$29,505.37	\$34,822.19

Dr. McCarthy reminded the Board of Regents that it had accepted recommendations of the Committee on Insurance regarding a new Professional Liability coverage, accepted through the Liberty Mutual Insurance Company of Boston. This contract went into effect on January 1, 1959, when coverage with Lloyds of London was terminated, in accordance with contract provisions. All new and renewal policies are being placed with Liberty Mutual. The Committee had held an official meeting with Officers of Liberty Mutual, the College counsel, the Group Insurance Administrators and the Executive Secretary, for the purpose of reviewing the Articles of Agreement. These were carefully analyzed, corrections or ambiguous statements were clarified, and both the Liberty Mutual and the College were in full and harmonious agreement. The final draft of the Articles of Agreement was reviewed by the College counsel, as well as by the Committee and by Mr. Joseph Linder, an insurance actuary of New York City. These Articles of Agreement were signed by the Executive Secretary, on behalf of the Committee and of the College, on February 18, 1959. On March 20, 1959, complete information was released to every member of the College, through a communication from the Executive Secretary, a descriptive pamphlet, including rates, and other data. Members were urged to communicate with the Group Insurance Administrators for clarification of any points in question. Dr. McCarthy stated that 560 policies had then been issued by Liberty Mutual, and that the Committee anticipated that there would be an ever increasing number.

He reminded the Board that this negotiation with Liberty Mutual was necessitated as a result of a sharp rate increase and restricted coverage by Lloyds. The new Liberty coverage is much broader and far more acceptable to the College. Dr. McCarthy explained that the title on the policy 'Physicians and Surgeons Professional Liability Policy' is required by State Insurance Departments, because any discrimination among specialty fields is not permitted by most State Insurance Commissions. The new Liberty Mutual policy and rates had been approved in all States, except Louisiana. The Committee is assured there is no question as to the legality of the coverage in all States. Dr. McCarthy recorded that Liberty Mutual rates, in some instances, may be slightly higher than rates offered by local insurance companies in some areas, but there may readily be a difference in the coverage provided. Liberty Mutual rates are filed at 10% below the rates of the National Bureau of Casualty Underwriters; a 15% year end dividend is currently being paid by Liberty Mutual and will be credited against the renewal premium for the following year, or will be paid to the policy holder, in the event of termination of coverage within a policy year.

This results in an overall saving of 23.5% on the National Bureau rates.

Liberty Mutual provides Professional Liability coverage starting at \$10,000/\$30,000 limits up to \$200,000/\$600,000 limits; it provides locum tenens coverage for sixty days in a policy year and will, in an emergency, extend this time upon proper

notification to the company.

On behalf of the Board of Regents, a panel of four nominees was submitted to the American Board of Internal Medicine for membership on that Board, for term expiring 1962 (from this panel, Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, was later chosen by the Board, to succeed Dr. Thomas M. Durant, F.A.C.P., Philadelphia).

Report, Committee on Standards of Hospital Practice in Internal Medicine: Dr. Arthur R. Colwell, Chairman, made a lengthy and detailed report, which is not repeated herein, because the conclusions of the Committee were included in an editorial published in the October, 1959, issue of the Annals of Internal Medicine.

RESOLVED, that the Board of Regents shall approve the recommendation that the Committee on Standards of Hospital Practice in Internal Medicine shall seek approval from the National Institutes of Health for the extension of the present grant for three months, from its present expiration of October 1, 1959, to January 1, 1960.

Dr. Colwell recorded that his Committee has no plans for continuation of the study beyond January 1, 1960, at which time the Committee plans to submit a final report and a firm recommendation to the Joint Commission on Accreditation of

Amendments to the Constitution and By-Laws: Proposed amendments to the Constitution and By-Laws were discussed generally among the Officers, Regents and Governors, and an agreement reached as to recommendations that would be presented at the Annual Business Meeting for adoption (details are not covered herein, because the completely amended and accepted Constitution and By-Laws will be published elsewhere).

Annual Business Meeting, April 23, 1959, Chicago:

Proceedings published in the June, 1959, issue (Volume 50, No. 6) of the Annals of Internal Medicine.

Board of Regents, April 24, 1959, Chicago:

In accordance with the new Constitution and By-Laws and by resolutions unanimously adopted, Dr. Wallace M. Yater was reëlected Secretary-General, for term expiring in 1962, and Dr. Thomas M. Durant was reëlected Treasurer, for term expiring in 1962.

It was recorded that under the new By-Laws, the maximal terms of the Secretary-General and of the Treasurer shall be four terms of three years each. The above regulations were recorded to have started as of this day, and that these officers shall be eligible for reelection, up to three additional terms.

RESOLVED, that all of the College Awards, Phillips, Bruce, Stengel and the A.C.P., be uniform, in that a certificate and a medal be awarded to each recipient.

On recommendation of the Committee on Publications, the following resolutions were adopted, concerning the Bulletin of the American College of Physicians:

RESOLVED, that the Committee on Publications and the newly appointed Editor, Dr. Thomas M. McMillan, shall be given authority to proceed.

RESOLVED, that \$6,000.00 shall be appropriated, to be available for expenses necessary to initiate the publication of the Bulletin of the American College of Physicians, to implement the work until November, 1959; any unexpended funds to revert to the new 1960 budget.

RESOLVED, that a fixed percentage of the subscription fee to the Annals or the amount of dues of members which is allocated to the Annals be designated as a subscription fee to the Bulletin; that the Bulletin be sent to all members of the American College of Physicians; that the Bulletin be sent upon request to those subscribers to the Annals who are not members of the College; that non-members of the College who do not subscribe to the Annals may subscribe to the Bulletin upon payment of the designated subscription fee.

It was suggested that up to \$1.00 of the dues of each member of the College be allocated for the purposes of the Bulletin; revenue from advertising and subscriptions shall be credited to the Bulletin account; the Board of Regents shall give to members of the American Society of Internal Medicine some indication as to the method of subscribing or receiving the Bulletin.

RESOLVED, that editorials which appear in the official publications of the College and which refer to organizational or administrative matters of the College shall be approved by the Committee on Publications before publication.

RESOLVED, that the Committee on Publications shall consist of seven members, composed of four Regents, two Governors and one member-at-large; Regents and Governors shall be eligible to hold office only so long as they shall be members of

the Board of Regents or of the Board of Governors; term of office shall be three years; members shall be eligible for reappointment; appointments shall be staggered so as to permit orderly replacement.

Report, Committee on Finance and Budgets: The annual financial report of the College has already appeared heretofore in a previous issue of this journal and is not repeated.

RESOLVED, that the Board of Regents approves the publication of the full proceedings of the Invitation Session, "The Care and Preservation of the American Executive," from the Chicago public meeting, to be paid for from the Michael Reese Fund, and that copies be distributed to the invited guests who were present, to Officers, Regents and Governors of the College, and that each essayist shall have the opportunity of reviewing and editing his material prior to publication.

RESOLVED, that the Southern California Traveling Scholarship Fund be returned to the Southern California group, with the understanding that it shall be administered by them, and any funds that may be issued to their local physicians or Associates for travel should not carry with it the name of the College.

RESOLVED, that the Committee on Educational Program of the College restudy the College's present policy with regard to paying travel expenses of contributors to the Annual Session program, and report back to the Regents in November, 1959, advice to be obtained from the Committee on Finance and Budgets as to the technical details and cost of extending allowances to Associates, as well as to non-members.

RESOLVED, that the Board of Regents shall approve the payment of traveling expenses of the President's wife to the Annual Sessions and to such Regional Meetings as he may attend and on which she accompanies him; the determination of whether she accompanies him or not shall be a matter of the President's judgment. This regulation shall become effective as of the date of adoption, April 24, 1959.

RESOLVED, that the Board of Regents refer to the Committee on Finance and Budgets the matter of payment of transportation of members of the Committee on Program of the Annual Session who are not already Regents or Governors, upon which they shall make a report to the Board of Regents at the November, 1959, meeting.

RESOLVED, that the Board of Regents direct the House Committee, along with the Executive Secretary, to make an immediate survey of the need and expansion of the College Headquarters building, and to report back to the Board of Regents at the November, 1959, meeting.

RESOLVED, that at Joint Sessions of the Regents and Governors nothing shall be considered which shall involve policy or change of policy; in other words, the agenda may cover anything that may be done within the framework of policy already established.

RESOLVED, that the title of Dr. Rolando Chanis be changed from Governor for Panama and the Canal Zone to Governor for the Republics of Central America and the Canal Zone.

RESOLVED, that the College Governor for Washington shall include in his jurisdiction Alaska, and that he shall be designated as the A.C.P. Governor for Washington and Alaska.

RESOLVED, that Dr. Donald F. Marion, F.A.C.P., Miami, Fla., be appointed General Chairman of the 42nd Annual Session, to be held at Bal Harbour, Fla., May 8-12, 1961.

Appointments and Elections to Committees of the College: In accordance with the new By-Laws and other regulations governing the functions, terms and appointments of committees of the College, all A.C.P. Committees for 1959-60 were recorded (list already published in a prior issue of this journal).



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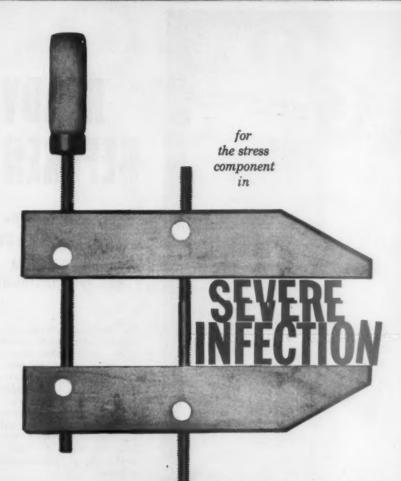


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Pyridoxine HCI (B <sub>6</sub> ) .			0	0	0		0	2 mg
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Calcium Pantothenate								
Vitamin K (Menadione)				a	0	0	0	2 mg

Average dose: 1-2 capsules daily.

- 1. Daskal, H. M.: Antibiotic Med. & Clin. Ther. 2:33 (June) 1956.
- Pollack, H. and Halpern, S. L.: Therapeutic <u>Nutrition</u>, National Research Council, Washington, D. C., 1952.



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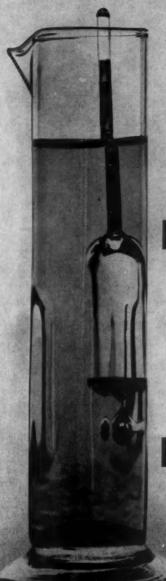






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1. Chamberlin, D. T.: Gastroenterology 17:224. 2. Hufford, A. R.: Am. J. Digest. Dis. 19:257. 3. Cholst, M., Goodstein, S., Berens, C and Cinotti, A.: J.A.M.A. 166:1276, 1958.

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## urinary discomfort, relieved within 30 minutes

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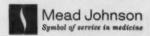
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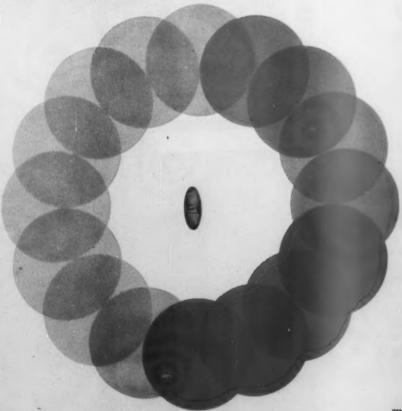
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Mead Johnson & Company, Evansville 21, Indiana 1. Feightner, R. L.: J. Indiana M. A. 51:1672-1674 (Dec.) 1958.





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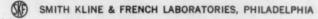


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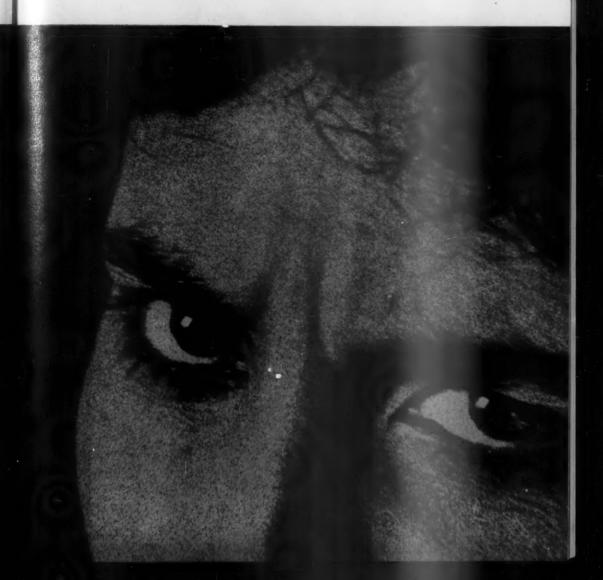
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Wennersten, J.R.: Clin. Med. 3:1179 (Dec.) 1956.
 Settel, E.: J. Am. Geriatrics
 Soc. 5:827 (Oct.) 1957.
 McAfoos, L.G., Jr.: Dis. Nerv. System 18:430 (Nov.) 1957.



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- (1) Mayer, G. A. and Connell, W. F. Connell, M.A.1. 77.93
- (2) Burke G. E. and Wright, 1. S. Circulation 3:164, 1951
- Keller, E. A.: Am. J. Med. 14.694, 1953.
- (4) Storrene, I. A. Birck, D. F. and Wright, J. S. Cirzole tion 6 489, 1952
- letten 15.713, 1957 (6) Fulta, F. R. Bartely, C. C. and Evans, J. A. J.A.M.A.
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1. Case reports on file, Wyeth Laboratories. 2. Parks, R.V., and Moessner, G.F.: Dual Approach to Patient Care, Scientific Exhibit, A.A.G.P., April, 1959.

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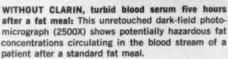
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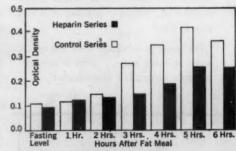
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- 1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
- Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959.



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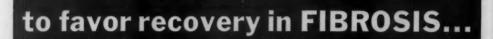
In searching for anticancer properties, Dr. Warren and his group will make 12,000 tests in the coming year. Many of these will use chemical substances produced at the Wyeth Institute for Medical Research. Many other tests will use fermentation products from the higher fungi, such as are shown here in the flasks. All materials passing the screen, as shown by growth inhibition or mouse-survival time, will be candidates for secondary study and eventual pharmacological evaluation for use in man.

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Evidence obtained from the observations of competent clinical investigators justifies the suggestion that this non-toxic drug may be found of great value wherever the pathological formation of fibrous tissue retards the patient's response to treatment.

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In 15 cases of Sarcoidosis cough, dyspnea and malaise decreased in 14. Partial or complete clearing of x-ray abnormalities was evident in 13 patients.<sup>1</sup>

21 Patients with Peyronie's disease receiving 12 gms. daily in divided doses for periods ranging from 3 months to 2 years responded as follows: Pain, where present disappeared from 16 of 16 cases. Penile deformity improved in 14 of 17 patients. Plaque decreased in 16 of 21.

#### POTABA DOSAGE FORMS





CAPSULES of 0.5 gm. (250's)



POWDER, 100 gm., 1 lb., 5 lb.



2 Gram sealed ENVELOPES (100's, 1,000's)



of 0.5 gm. (100's, 1,000's)

Complete literature available to physicians on request.
Also available: Information on PASKALIUM (Pure Potassium P.A.S.).
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- visualization of the kidneys and urinary passages including the renal pelves, ureters and bladder — within 5 to 15 minutes.
- IN CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY
- visualization of the hepatic and common ducts in 10 to 15 minutes even in cholecystectomized patients
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Duografin spares the patient from superfluous radiation exposure...is extremely well tolerated... saves time for both physician and patient. In 25 patients Duografin was administered for simultaneous urography and cholecystocholangiography. "Most of the patients showed excellent visualization of both tracts." Duografin is "... of special value in acute cases... It also saves time and avoids the necessity of two separate preparations for routine radiological study." Garfinkel, B., and Furst, N.J.: Radiology 70:243 (Feb.) 1958.

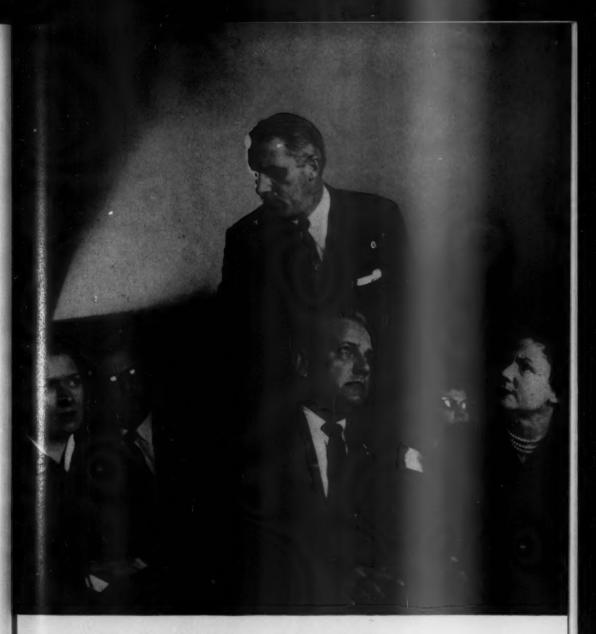
Duografin: Supplied as a sterile aqueous solution for intravenous injection, providing 40% distrizoate base (3,5-diacetylamino-2,4,6-trilodobenzoic acid) and 20% iodipamide base (N,N-adipyl-bis 3-amino-2,4,6-trilodo benzoic acid), both in the form of their methylglucamine salts. The solution contains approximately 38% firmly bound iodine; in vials of 50 cc.

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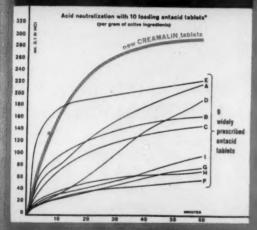


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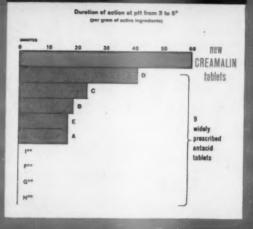
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## RESULTS IN 366 PATIENTS WITH STOMACH ULCERS

DIAGNOSIS	TOTAL	MARKED IMPROVEMENT WITH X-RAY GAINS	MARKED IMPROVEMENT	SLIGHT IMPROVEMENT	NO IMPROVEMENT
PEPTIC	50	10	29	9	2
GASTRIC	56	11	33	10	2
DUODENAL	256	39	175	33	9
PYLORIC	4	-	1	2	1
TOTAL	366	60	238	54	14
Summary of investigators'	reports.	16%	65%	15%	4%

#### REPORTED BY PATIENTS, CONFIRMED BY X-RAY, 81% MARKED IMPROVEMENT IN STOMACH ULCER

proven relief of pain, spasm and nervous tension without the side effects of belladonna, bromides or barbiturates

#### INDICATIONS-

duodenal and gastric ulcer
gastritis
colitis
spastic and irritable colon
gastric hypermotility
esophageal spasm
intestinal colic
functional diarrhea
G. I. symptoms of anxiety states

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POLANIL

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POLANIL is dextro-chlorpheniramine maleate (Polaramine Maleate) — the closest to a perfect antihistamine and dexamethasone (Deronil\*) — today's lowest dosage corticosteroid.

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in surgery, hospitalized or inactive patients

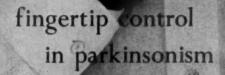
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Bec use Parsidol excels in control of tremor and muscular rightity<sup>1,2</sup>, many routine chores of the parkinsonian patient are made easier. Activities not even attempted before, are made cossible because Parsidol permits increased freedom of movement even at the fingerlips.

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- 1. Schwab, R.S. and England, A.C.: J. Chron. Dis.
- 8:488-509 (Oct.) 1958.
- 2. Doshay, L.J. et al.: J.A.M.A. 160:348 (Feb.) 1956.

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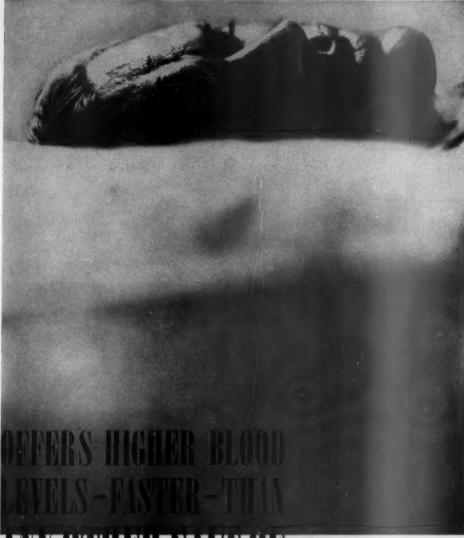


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References:
1. Campbell, M. F.: Principles of Urology,
Psiladelphis, W. B. Saunders Company, 1957,
p. 232. S. Sophisn, L. H., Friger, D. L., and
New York, A. Colish, 1958, pp. 70-76.
3. Lehr, Da New York J. Med. 50:1361
(June J. 1958)





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References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

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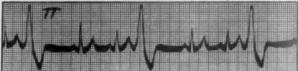
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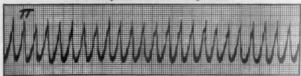
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proven calming action indicated for arrhythmia patients.

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References: 1. Burrell, Z. I., et al.: Am. J. Caydiol., 1:624 (May) 1958. 2. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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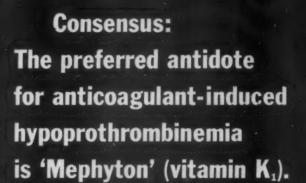
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(1) Gross, H., and Jezer, A.: Treatment of Heart Disease, Philadelphia, W. B. Saunders Company, 1956, p. 41. (2) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2., New York, The Macmillan Company, 1956, p. 698.(3) Modell, W.: Drugs of Choice 1958-1959, St. Louis, C. V. Mosby Company, 1958, p. 441.

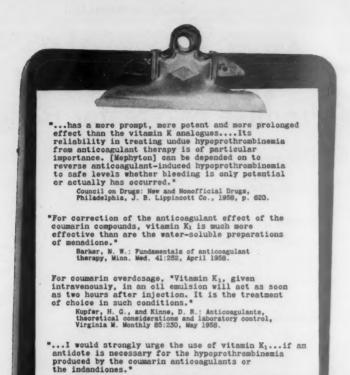
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Meyer, 0. 0.: Use of anticoagulants in the treatment of coronary artery disease, Postgrad. Med. 24:110, Aug. 1958.

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Previous Therapy:

40 mg. tri mcinalone par day.

Complication States:

Duodenal pleer, steroid intoxication.

Current Therapy: ARTHROPAN Liouid

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Each ml. of ARTHROPAN Liquid contains
174 mg. of Choline Salicylate.

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1. Clark, G.M.: Personal Communication, 1958.

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for prolonged, physiologic relief conditions...whether you use

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... is the ACTH preparation of choice (2) to revitalize the adrenal cortex and systemic corticosteroid therapy, and

Repository corticotropin may be administered periodically "to minimize adrenal suppression and atrophy in patients receiving long-term therapy with corticoids ... and particularly when corticoid withdrawal is started."<sup>2</sup>

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Contraindications: Those of ACTH: long-term treatment in hypertension, diabetes mellitus, mental disturbances, chronic nephritis, congestive heart failure, Cushing's syndrome, hirsutism.

References: 1. Thorn, G. W., et al.: Report to the Council on Drugs, J.A.M.A. 168:2130, 1958.

2. Segal, M. S.: Current Status of Therapy in Bronchial Asthma (Report to the Council on Drugs), J.A.M.A. 169:1063, 1959.

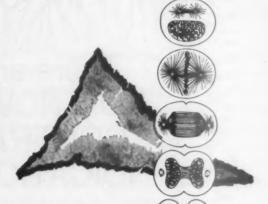
3. Siegel, S. C.: Lederle Symposium Report, 1:43, 1958.



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of asthma, hay fever, and other allergic ACTH or corticosteroids, or both...

# -Zinc hydroxide (Organon)



(1) for dramatic relief of allergic symptoms, protect its functional integrity during

(3) to prevent "iatrogenic adrenal insufficiency"1

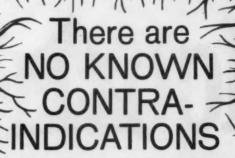
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References: 1. M. M. Fisher and H. E. Tebrock: New York State J. Med. 53:65, 1953. 2. R. O. Gilhespy: Brit. M. J. 1:207, 1957. 3. E. C. Texter, et al.: Am. J. Med. Sc. 221:408, 1952. 4. W. Redisch and O. Brandman: Angiology 1:312, 1950. Complete bibliography available on request.

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SIGNIFICANT
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DEPLETION

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NEW

REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 52:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267

(May) 1959. LITERATURE AVAILABLE ON REQUEST



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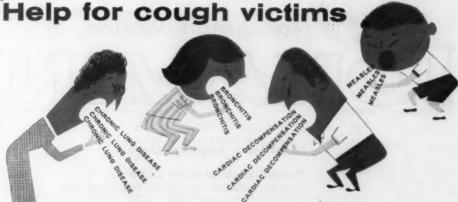
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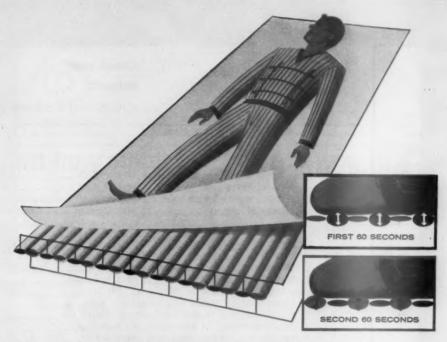
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HEMATOLOGY

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may be either ineffective or poorly tolerated. To
date, there is no evidence that this agent is of any
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DOSAGE Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature \* accompanying each package.

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UNITENSEN: BASIC HYPERTENSIVE THERAPY Although many of the patients in the Study also received diuretics and/or tranquilizers

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\*Cohen, B. M.: The Ambulatory Patient with Hypertension: An Approach to Office Management, presented at the American Medical Association Convention, San Francisco, California, June 22-27, 1988.

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# Schedule of Postgraduate Courses, Autumn-Winter, 1959-1960 THE AMERICAN COLLEGE OF PHYSICIANS

		October	per			Nov	November			Dece	December	_		January	ary	1044	February
The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Customary tuition fees will be: Members, \$60,00; Non-members, \$80,00. Full states of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.	Sept. 28-Oct. 2	13-16	19-23	76-30	9-7	£1-6	16-20	23-27 30-Dec. 4	11-4	81-11	21-25	1 .nsl-82	8-1	21-11	18-22	52-53	21-8
Course No. 1, INTERNAL MEDICINE: Georgetown University School of Medicine, Washington, D. C.; Laurence H. Kyle, M.D., FA.C.P., and Hugh J. Hussey, Jr., M.D., F.A.C.P., Directors. CONCLUDED - Registration 8150.	×							1	1						1		
Course No. 2, SELECTED SUBJECTS IN INTERNAL MEDICINE: The University of Buffalo School of Medicine, Buffalo, N. V.; John H. Talbott, M.D., F.A.C.P., Director, WITHDRAWN	1	8,0,0,0						1	1				1	1			
Course No. 3, THE SCIENCE OF INTERNAL MEDICINE: State University of New York Upstate Medical Center, Syracuse, N. Y.; Richard H. Lyons, M.D., F.A.C.P., Director.					×		-100/1	Veek	1		ek	1			1	1	1
Course No. 4, CLINICAL CARDIOLOGY: Tulane University School of Medicine, New Orleans, La.; George E. Burch, Jr., M.D., F.A.C.P., Director.						1		× Suiati	1		W asm			1	1	+	-
Course No. 5. CURRENT CONCEPTS OF THE RHEUMATIC DISEASES—THEIR RECOGNITION AND MANAGEMENT: Cornell University Medical College and The Hospital for Special Surgery, New York, N. Y.; Richard H. Freyberg, M.D., F.A.C.P., Director.	1	1					1-40	Thanks	1	1	Christ			×			1
Course No. 6, INTERNAL MEDICINE—Selected Subjects: Henry Ford Hospital, Detroit, Mich., John G. Mateer, M.D., F.A.C.P., Director,			1		1	1	1							1	1	×	1
Course No. 7, RECENT ADVANCES IN METABOLIC DISEASES: The Mount Sinai Hospital, New York, N. Y.; Alexander B. Gutman, M.D., F.A.C.P., Director.	1	1	-			1	1	1	1	-			1	1	1	1	×



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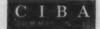
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Lethargy or fatigue	5	5	0
Nasal congestion	7	7	0
Gastrointestinal disturbances	2 .	0	2
Conjunctivitis	. 1	1	0

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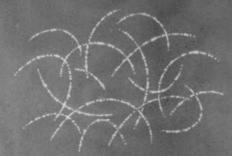
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I. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

2. Bartels, C. C. Clinical report to CIBA.

#### INDEX TO ADVERTISERS OCTOBER, 1959

Abbett Laboratories	Tracet facing 80, 11, 66, 125
Abbott Laboratories	100
A. I. M. Are you moving?	78
A. I. M. Subscriptions	104
A. I. M. Wanted Back Issues	4 98
Air Mass, Inc. (Div. R. D. Grant Company)	488
Ames Company, Inc.	10 19
Armour Pharmaceutical Company	
Astra Pharmaceutical Products, Inc.	11, 91
Ayerst Laboratories	29, 38, 106
Borcherdt Company	
Burroughs Wellcome & Co. (U.S.A.), Inc.	
Carnation Milk Company	60
Ciba Pharmaceutical Products, Inc.	54–55, 164–165
Warren E. Collins, Inc.	4
Davies, Rose & Company, Limited	
Eaton Laboratories	
Endo Laboratories	
C. B. Fleet Company, Inc.	82
E. Fougera & Company	
Geigy Chemical Corporation	
General Electric Company	
Glenwood Laboratories	
Grune & Stratton, Inc.	5
Paul B. Hoeber, Inc.	8
Hyland Laboratories	
Irwin Neisler & Company	
Lea & Febiger	6
Lederle Laboratories, Div. American Cyanamid Co	
Thos. Leeming & Company	
Eli Lilly & Company	
Lloyd Brothers, Inc.	6, 128
Macmillan Company, The	
McNeil Laboratories, Inc	
Mead Johnson & Company	20-21, 107
Merck Sharp & Dohme 14, 34-	-35, 50-51, 71, 96, 184, 144-145
Wm. S. Merrell Company, The	64, 102
Organon, Inc	
Pet Milk Company	
Pfizer Laboratories, Div. Chas. Pfizer Co. Inc	nsert facing 64, 24, 84-85, 141
Pharmacia Laboratories, Inc.	
Pitman-Moore Company	
Purdue Frederick Company, The	
Michael Beese Hospital	93
Riker Laboratories, Inc.	Second Cover 22 53 168
Ritter Company, Inc.	
A. H. Robins Company	16 74 109_109
Roche Laboratories, Div. Hoffmann La Roche, Inc.	10 96 97 44 45 191 150
J. B. Roerig & Company	20 40 40 00 00
Wm. H. Rorer, Inc.	115
Sanborn Company	104
Sandor Pharmaceuticals	Togget facing 99
Schering Corporation	
Schieffelin & Co.	
C. D. Sanda & Co.	
G. D. Searle & Co	49 00 01 100 100 110
E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. 12, 30, 58-50,	E 76 77 AE 190 100 181 161
E. K. Squidd & Sons, Div. Olin mathieson Chemical Corp. 12, 50, 55-50, 6	10, 10-11, 90, 120, 100, 101, 101
R. J. Strasenburgh Co	
Travenol Laboratories, Inc. Div. maxter Laboratories, Inc.	
Upjohn Company, The	
U. S. Vitamin Corporation	162–163
Wallace Laboratories 9, 28, 3	5, 37, 83, 89, 112, 126, 158-159
Wampole Laboratories	
Warner-Chilcott Laboratorles	7, 30-31, 40, 101, 103, 105, 129
White Laboratories, Inc	Insert facing 8, 67, 68-69
Winthrop Laboratories, Inc.	
Woodward Medical Personnel Bureau	
Wyeth Laboratories 15, 22, 47, 52, 61,	81, 111, 116-117, 121, 146, 167
Wynn Pharmacal Corporation	70



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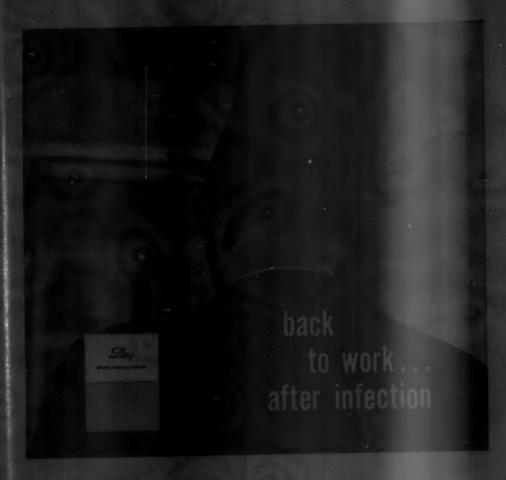
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